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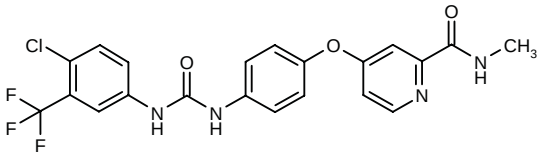
Bay-43-9006

Oncolytic
Raf Kinase Inhibitor

4-[4-[3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido]phenoxy]-*N*-methylpyridine-2-carboxamide



$C_{21}H_{16}ClF_3N_4O_3$
Mol wt: 464.8294
CAS: 284461-73-0
EN: 301618

Abstract

The Ras/Raf/MEK pathway is a signaling module that controls cell growth and survival. Activation of this pathway results in a cascade of events from the cell surface to the nucleus ultimately affecting cellular proliferation, apoptosis, differentiation and transformation. Raf is a serine/threonine kinase that is a downstream effector enzyme of Ras. When activated, Raf goes on to activate MEK1 and MEK2 kinases which in turn phosphorylate and activate ERK1 and ERK2 which translocate to the nucleus where they stimulate pathways required for translation initiation and transcription activation leading to proliferation. Raf kinase has been validated as a potential and attractive target for hyperproliferative disorders such as cancer. Research has recently focused on efforts to discover potent Raf kinase inhibitors and several low-molecular-weight Raf kinase inhibitors have been described. Bis-aryl ureas were identified within this program using medicinal chemistry-directed syntheses or combinatorial libraries. After high-throughput screening of more than 200,000 compounds against recombinant Raf-1 kinase, the orally active Bay-43-9006 was identified as having potent inhibitory activity and was chosen for further development as a treatment for cancer. Bay-43-9006 has exhibited potent *in vitro* activity against several tumor cell lines and has displayed efficacy in human tumor xenograft models. Moreover, results from phase I development in patients with a variety of cancer types indicates promising clinical efficacy for the compound.

Synthesis

Reaction of picolinic acid (I) with hot thionyl chloride in DMF gives 4-chloropyridine-2-carbonyl chloride (II), which is treated with methanol to give ester (III). Subsequent displacement of the methyl ester function with methylamine provides amide (IV). Alternatively, acid chloride (II) is directly converted into amide (IV) by reaction with a cold solution of methylamine. In a different synthetic procedure, amide (IV) can be obtained from 4-chloropyridine (V) via the Menisci reaction using *N*-methylformamide and hydrogen peroxide in the presence of $FeSO_4$ and H_2SO_4. Coupling of the amide (IV) with potassium 4-aminophenolate (VI) – obtained by treatment of 4-aminophenol (VII) with potassium *tert*-butoxide – in hot DMF yields the pyridyloxyaniline (VIII). Aniline (VIII) is finally condensed with either 4-chloro-3-(trifluoromethyl)phenyl isocyanate (IX) in CH_2Cl_2 (1-3) or 4-chloro-3-(trifluoromethyl)aniline (X) by means of CDI in CH_2Cl_2 (3). Scheme 1.

Introduction

The Ras/Raf/MEK (MEK: MAP/ERK kinase; ERK: extracellular signal related kinase) pathway is a signaling module that controls cell growth and survival. Activation of this pathway results in a cascade of events from the cell surface to the nucleus ultimately affecting cellular proliferation, apoptosis, differentiation and transformation. This crucial signaling pathway is frequently found to be altered in human cancers, directly controlling formation and progression of tumors. Moreover, in human tumors, mutant ras oncogenes which permanently switch on Ras are associated with disease progression. Thus, inhibition of the Ras/Raf/MEK signaling cascade represents an extremely attractive target for the treatment of hyperproliferative disorders such as cancer (4-10).

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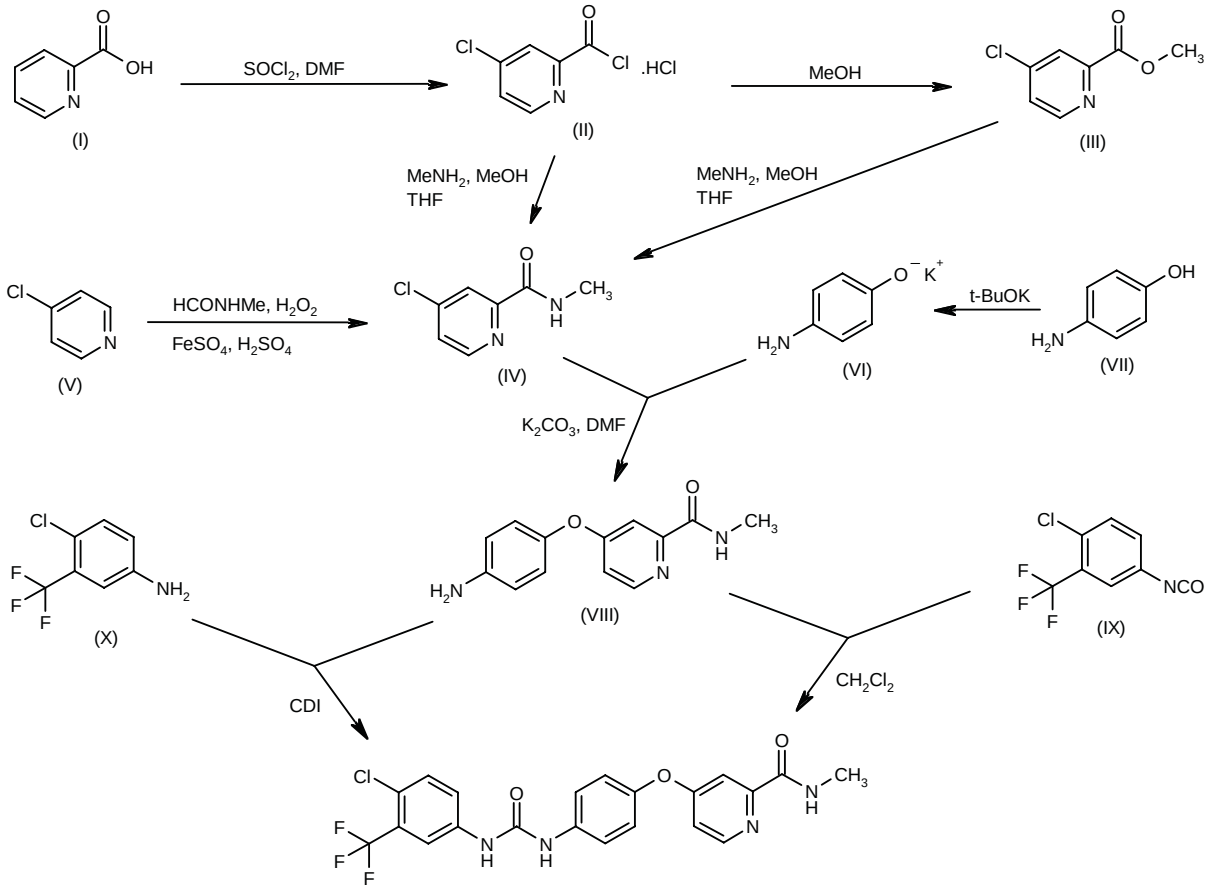
Scheme 1: Synthesis of Bay-43-9006



Ras belongs to a large family of GTPases and its activity is modulated via the interaction of GTP exchange factors (GEFs) and GTPase activating proteins (GAPs). To be switched on, whether through a mutational event or growth factor receptor activation, Ras requires dissociation from GDP via several protein-protein interactions thus allowing it to bind GTP. The Ras/GTP complex then activates a kinase cascade through the Raf/MEK/ERK module. This results in modulation of transcription factors such as CREB and proapoptotic module such as BAD (Fig. 1).

Raf is a serine/threonine kinase that is a downstream effector enzyme of Ras and an excellent target for cancer therapy. There are 3 members of the Raf family: Raf-1 (or C-Raf), A-Raf and B-Raf. Activation of Raf involves several steps including Raf-1 phosphorylation, binding of the Raf protein to the Ras/GTP complex, oligomerization of the Raf protein, association with other proteins (*e.g.*, heat shock and 14-3-3 proteins), interactions of the Raf protein with membrane lipids and conformational changes of the Raf protein induced by Ras. Activated Raf goes on to activate MEK1 and MEK2 kinases which in turn phosphorylate and activate ERK1 and ERK2. Activated ERK family members translocate to the nucleus where they stimulate pathways required for translation initiation and transcription activation leading to proliferation. Raf kinase has been validated as a potential target for cancer therapy. Studies have shown that genetic inhibition of the Raf/MEK pathway decreases endogenous activity of the module, inhibits anchorage-dependent tumor cell growth and suppresses tumor progression in mice (11-13).

Several attempts have been made in efforts to discover potent Raf kinase inhibitors and several low-molecular-weight Raf kinase inhibitors have been described. Benzylidene indolinones have been reported to be effective Raf kinase inhibitors with activity seen *in vivo* in tumor xenografts. However, amides such as ZM-336372 did not exhibit good *in vitro* activity and other triaryl imidazoles such as L-779450 were active *in vitro* but lacked *in vivo* efficacy (14-17). A more promising novel class of small-molecule inhibitors of Raf-1 kinase have been discovered

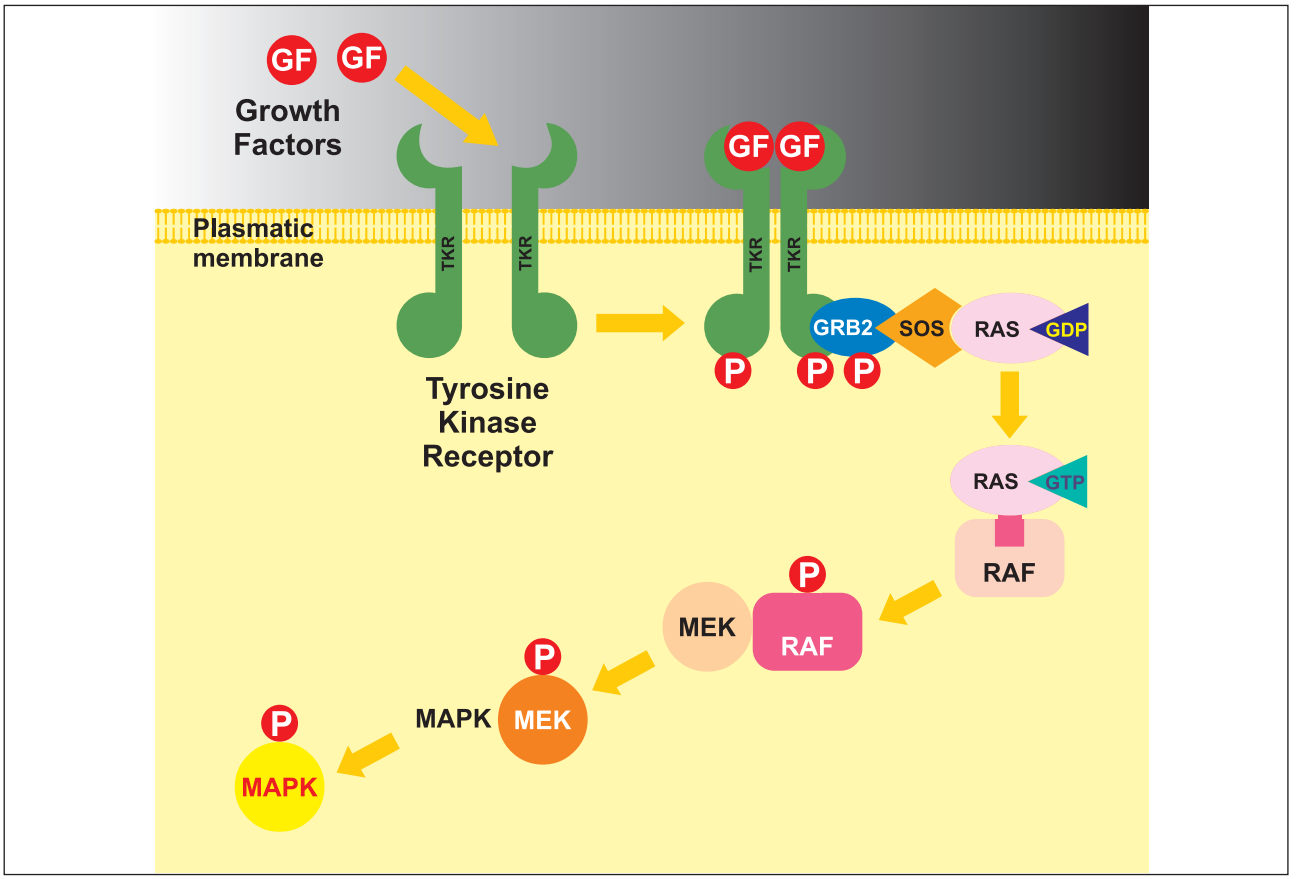


Fig. 1. The Ras/Raf/MEK signaling pathway.

(13, 18). These compounds are bis-aryl ureas and were identified through medicinal chemistry-directed syntheses or combinatorial libraries. After high-throughput screening of more than 200,000 of these compounds against recombinant Raf-1 kinase, the orally active Bay-43-9006 was identified as having potent inhibitory activity and was chosen for further development as a treatment for cancer (18).

Pharmacological Actions

Bay-43-9006 displayed potent inhibitory activity against recombinant human Raf-1 kinase, with an IC_{50} value of 12 nM obtained. *In vitro* experiments using tumor cell lines have demonstrated that Bay-43-9006 does not directly inhibit MEK-1 or ERK-1. However, Bay-43-9006-induced inhibition of Raf-1 kinase resulted in reduced MEK-1 and ERK-1 phosphorylation (18, 19). The agent was shown to inhibit endogenous MEK-1 activation in estrogen-stimulated NIH 3T3 cells expressing a chimera of b-Raf-1 protein in addition to the hormone binding domain of the estrogen receptor. In addition, experiments using a colon cancer cell line (HCT 116) incubated with epidermal growth factor (EGF) to stimulate the endogenous Raf/MEK/ERK module, showed that inhibition of ERK phosphorylation was modulated by Bay-43-9006. The agent was also effective in inhibiting basal ERK phosphorylation in proliferating HCT 116 cells (20, 21). Proliferation of adherent HCT 116 cells and nonadherent pancreatic cancer cells (Mia PaCa-2) was also inhibited by *in vitro* treatment with Bay-43-9006. The agent significantly reduced tumor cell proliferation at doses known to inhibit Raf activity (20, 21). Proliferation of imatinib-resistant chronic myelogenous leukemia cell lines was also markedly inhibited by the agent (IC_{50} = 4-8 mM) with reductions in ERK phosphorylation noted with treatment (22).

The *in vitro* antitumor efficacy of Bay-43-9006 has also been demonstrated in combination with other cytotoxic agents. One study using colon carcinoma cells (HCT 8, HCT 29 and HCT 116) with or without targeted deletion of the p53 gene, examined the cytotoxic efficacy of the agent in combination with paclitaxel, 5-FU or SN-38 after 48 h of incubation. Bay-43-9006 was effective in all stages of the cell cycle regardless of p53 genotype and was also cytotoxic against SN-38-resistant HCT 8 and HCT 29 cells. Results from combination treatment studies revealed antagonism when Bay-43-9006 was administered in tandem with paclitaxel or SN-38. However, when

sequential scheduling was used where cells were initially treated with paclitaxel or SN-38 and subsequently treated for 48 h with Bay-43-9006, weak or moderate synergy was observed. Additivve antitumor activity was observed when a protracted schedule was employed involving treatment with Bay-43-9006 on day 1 followed by combination treatment with Bay-43-9006 and SN-38 on day 2 and subsequent treatment with Bay-43-9006 on days 3 and 4 for another 48 h (23).

Bay-43-9006 also displayed potent antitumor growth effects in vivo in experiments using nude mice implanted s.c. with established (100-200 mg) HCT 116, Mia PaCa-2 or non-small cell lung cancer (NSCLC; NCI-H460) tumors all containing K-ras mutations or established ovarian tumors (SK-OV-3) which have a wild-type ras genotype but overexpress EGF and Her-2 receptors resulting in constitutive activation of Raf/MEK/ERK pathway. Potent dose-dependent inhibition of tumor growth was observed for all 3 human tumor types when Bay-43-9006 was administered orally for 14 days. In the HCT 116 human xenograft model, reductions in tumor growth of 45, 64 and 68% were seen with doses of 10, 30 and 100 mg/kg, respectively; comparable results (44, 66 and 73%, respectively) were obtained in the Mia PaCa-2 human xenograft model. NCI-H460 tumor growth was inhibited by 27% and 56% with doses of 10 and 30 mg/kg, respectively. However the SK-OV-3 model was the most sensitive, with growth inhibition ranging from 45-81% seen at doses of 3-100 mg/kg. These results indicated that the efficacy of the agent does not require the ras oncogene. In the HCT 116 model, Bay-43-9006 (30 and 100 mg/kg) produced net tumor stasis when treatment was continued for 30 days. Furthermore, monitoring of tumors for 14 days after discontinuation of dosing in animals treated with 10, 30 or 100 mg/kg Bay-43-9006 revealed significantly reduced tumor sizes as compared to controls. These results suggest that the effects of the agent are maintained even after cessation of treatment. Bay-43-9006 (3, 30, and 100 mg/kg p.o. once daily for 14 days) was also effective in significantly slowing tumor growth in animals with advanced stage established (about 1 g) HCT 116 tumors (20, 24).

The *in vivo* efficacy of Bay-43-9006 (40 or 80 mg/kg p.o.) in combination with irinotecan (40 mg/kg), vinorelbine (6.7 mg/kg) or gemcitabine (120 mg/kg) was examined in a study using athymic mice with DLD-1 colon, NCI-H460 or Mia PaCa-2 established (10-120 mg) s.c. tumors. Bay-43-9006 (80 mg/kg) was administered p.o. daily for 9 days while the other agents were given intermittently (i.p. or i.v.) every 4 days for 3 courses. All combination therapies were well tolerated with no significant toxicity observed. In mice bearing DLD-1 tumors, monotherapy with Bay-43-9006 (80 mg/kg) or irinotecan resulted in tumor growth delays of 100 and 71%, respectively. However, combination treatment caused a tumor growth delay of 229%. Mice bearing NCI-H460 tumors and treated with Bay-43-9006 (40 mg/kg) or vinorelbine alone showed tumor growth delays of 104 and 32%, respectively, while combination therapy resulted in a growth delay of 133%. Treatment of mice bearing Mia PaCa-2 tumors with Bay-43-9006 (40 mg/kg) and gemcitabine alone produced tumor growth delays of 112 and 154%, respectively, while combination treatment caused a 221% growth delay (25).

Clinical Studies

A phase I, dose-escalation study was conducted in patients with refractory solid cancers (colorectal, breast, renal, head and neck, melanoma and others) to determine the maximum tolerated dose (MTD), dose-limiting toxicity (DLT) and pharmacokinetics of oral Bay-43-9006 (50 mg once daily on days 1, 5, 10, 15 and 20 or days 1, 3, 5, 7, 9, 11, 13, 15, 17, 19 and 21; or 100, 200, 300, 400, 600 or 800 mg b.i.d. daily for 3 weeks with a 1-week rest period). A total of 38 patients were evaluable. The toxicities seen which were all rapidly reversible were anorexia, fatigue, diarrhea, alopecia and skin toxicities (rash, hand and foot syndrome, folliculitis and dryness). The skin toxicities limited dose escalation and warranted dose reductions in patients at the 600 and 800 mg dose levels. No myelosuppression was reported. Steady state was reached after 7 days of dosing. Linear increases in C_{max} and AUC values were observed at doses up to 300 mg b.i.d. while only modest increases were observed thereafter. The terminal $t_{1/2}$ after day 21 was between 30 and 45 h regardless of the dose level. Three patients (2 renal and 1 rectal) starting at 600 mg experienced tumor shrinkage of 20%; 1 renal cancer patient achieved a partial response. Three patients (2 colon, 1 head and neck) had stable disease for more than 4 months. Accrual is ongoing at 400 mg b.i.d. in 10 patients (26).

Final results from a phase I, dose-escalation trial conducted in 37 patients with advanced refractory solid tumors (ovary/abdominopelvic, colon, pancreas, renal, breast and other) have been presented. The study was initiated to determine the MTD, toxicity profile and pharmacokinetics of oral Bay-43-9006 administered at doses of 50 mg twice weekly every other day or once daily, 100 mg once daily or 100, 200, 400 or 600 mg b.i.d. daily for 28 days of a 25-day cycle. A total of 101 cycles were completed. Twenty-eight patients are off the study due to adverse events (6 patients), disease progression or death (21 patients) or for other reasons (1 patient). The MTD was reached. Most toxicities reported were mild (grade 1-2) and included dermatologic events (31 cases), dyspepsia (7 cases), flatulence (8 cases), diarrhea (7 cases), nausea (5 cases), anorexia (5 cases), fatigue (9 cases), pain (5 cases), neurological events (6 cases), alopecia (3 cases) and insomnia (2 cases). Grade 3 toxicities observed were abnormalities in ALP (8 cases), lymphocytes (8 cases), bilirubin (5 case) and AST/ALT (5 cases) and hyponatremia (10 cases). Three patients on 600 mg b.i.d. daily developed foot and hand syndrome. A 1.6- to 9-fold accumulation in the $AUC_{0-\tau}$ value was observed from day 1-28 indicating accumulation of the agent with

multiple dosing. Three patients have had tumor shrinkage of at least 20% to date (27). Within this study, a novel flow cytometry method involving phospho-specific antibodies was employed in an attempt to measure Raf activation of ERK1/2 in peripheral blood T-lymphocytes from patients. Preliminary results were obtained from 17 patients administered 50 mg every other day up to 100 mg daily. Activation indices after 28 days of treatment from 4 patients treated with the higher dose level were 15 ± 3.22 as compared to 19.5 ± 4.05 before dosing (28).

The final results of a phase I trial involving 62 advanced stage cancer patients (PS 0-2, mostly heavily pretreated) with refractory malignancies (colorectal, hepatocellular, breast, NSCLC and others) treated with oral Bay-43-9006 (100, 200, 400 and 800 mg b.i.d. starting with weekly doses followed by continuous daily treatment) have been reported. The DLT was grade 3 diarrhea seen in 2 of 6 patients treated with 800 mg b.i.d. daily. Other toxicities that were not dose limiting included grade 1-2 rash in 9 patients on 200 mg b.i.d. daily, grade 3 pancreatitis in 1 patient on 100 mg b.i.d. daily and grade 2-3 fatigue in 2 patients on 800 mg b.i.d. daily. Prolonged stabilization of more than 3 months was seen in 20 patients (32%) with previous progressive disease. The median time to tumor progression was 9+ and 16.3+ weeks in patients with colorectal and hepatocellular cancer, respectively. A partial response (47+ weeks) was seen in a patient with hepatocellular cancer treated for 20 weeks with 400 mg b.i.d. daily. Steady state was achieved after 7 days of dosing. $AUC_{0\text{-}12\ h}$ at steady state, C_{max} and t_{max} values at the 400 mg b.i.d. daily dose level were 73 mg·h/l, 9.9 mg/l and 1.75 h, respectively (29). Analysis of inhibition of ERK phosphorylation of patient peripheral blood lymphocytes (PBLs) using flow cytometry with phospho-specific antibodies revealed significant inhibition of PMA-stimulated CD7 positive T cells in 4 of 6 patients on 200 mg b.i.d. daily, 6 of 14 patients on 400 mg b.i.d. daily and 6 of 6 patients on 800 mg b.i.d. daily. The time course and degree of inhibition of ERK phosphorylation was found to be correlated with Bay-43-9006 dose (30).

A phase I study involving 15 patients with locally advanced or metastatic cancer (PS 0-2) examined the pharmacokinetics and efficacy of oral Bay-43-9006 (one dose of 50-400 mg once/week or 100 mg b.i.d. or t.i.d. once/week p.o.). Pharmacokinetic parameters were obtained in fasted and fed states. No toxicities were observed to date. Two patients with hepatocellular cancer experienced stable disease lasting for 5+ months and 1 patient with colorectal cancer had stable disease for 4+ months. Food intake did not alter absorption of the agent. However, daily splitting of doses (*e.g.*, 100 mg b.i.d. or t.i.d.) increased exposure. C_{max} and AUC values for doses of 50-400 mg ranged from 0.74-3.6 mg/l after 2-14 h and 19-110 mg·h/l, respectively. Accrual is ongoing (31, 32).

The safety and efficacy of oral Bay-43-9006 (100 or 200 mg daily [Group A] for 28 days or b.i.d. daily [Group B] for 14 days every 28 days) were examined in a randomized, phase I trial involving 19 patients with myelodysplastic syndrome or acute myeloid leukemia. The median number of cycles administered to date is 1. The most common drug-related toxicities observed were (Group A *vs.* B) diarrhea (20 *vs.* 33%), abdominal pain (50 *vs.* 22%), stomatitis (10 *vs.* 22%), nausea (20 *vs.* 22%), vomiting (20 *vs.* 0%) and dyspnea (0 *vs.* 22%); no case of rash was seen. One patient in group B showed a reduction in blast count from 80% to 40% indicating preliminary biological activity. In addition, preliminary data from 6 patients show that ERK phosphorylation was reduced with treatment. Accrual is ongoing at 400 mg b.i.d. (33).

Bay-43-9006 is currently undergoing trials in combination with other chemotherapeutic agents to determine its tolerability as a treatment for several cancer types. Phase II and III trials in cancer patients are planned to determine the safety and efficacy of these combination therapies (34).

Source

Bayer AG (DE) in codevelopment with Onyx Pharmaceuticals, Inc. (US).

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