Published in final edited form as:
IDrugs. 2010 February ; 13(2): 112–121.

XL-184, a MET, VEGFR-2 and RET kinase inhibitor for the treatment of thyroid cancer, glioblastoma multiforme and NSCLC

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Abstract

XL-184 (BMS-907351), under development by Exelixis Inc and Bristol-Myers Squibb Co, is a pan-tyrosine kinase inhibitor for the potential oral treatment of medullary thyroid cancer, glioblastoma multiforme and NSCLC. The prinicipal targets of XL-184 are MET, VEGFR-2 and RET, but the drug is also reported to display inhibitory activity against KIT, FLT3 and TEK. Preclinical studies demonstrated that XL-184 potently inhibited multiple receptor tyrosine kinases in various cancer cell lines and animal xenograft models, and that the drug exhibited significant oral bioavailability and blood-brain barrier penetration. A phase I clinical trial in patients with advanced solid malignancies indicated that XL-184 accumulated dose-dependently in the plasma and had a long terminal half-life. A phase II trial in patients with progressive or recurrent glioblastoma revealed modest but promising median progression-free survival. Toxicity and side effects for the drug have generally been of low-to-moderate severity. At the time of publication, three additional trials of XL-184 were recruiting patients, including a phase I trial in combination with standard of care in patients with glioblastoma, a phase I/II trial in combination with erlotinib in patients with NSCLC, and a phase III trial in patients with medullary thyroid cancer.

Introduction

Receptor tyrosine kinases (RTKs) are a large family of cell surface receptors that are endowed with intrinsic protein tyrosine kinase activity. These kinases are activated by various ligands and play an important role in the control of most fundamental cellular processes, including activity in the cell cycle, cell migration, cell metabolism and cell survival, as well as cell proliferation and differentiation. The effects of RTKs are mediated by a complex network of cell signaling cascades, the most well known of which are the RAS/MAPK and PI3K/AKT pathways [1059444]. Aberrant activation of RTKs can occur via ligand and/or receptor transcriptional overexpression, gene amplification, activating mutations or epigenetic mechanisms, and leads to enhanced malignancy in a wide variety of cancers, including medullary thyroid cancer (MTC), glioblastoma multiforme (GBM) and NSCLC [1052976], [1059446], [1059447].

MTC is a neuroendocrine tumor that originates in the calcitonin-producing parafollicular (C cells) of the thyroid [1059455]. Standard treatment consists of surgery and radiation, and

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serum levels of calcitonin and carcinoembryonic antigen, both of which are often elevated in patients with MTC, are used to monitor disease progression. MTC accounts for 5 to 10% of all thyroid malignancies; in approximately 60% of cases, MTC Therapeutic XL-184 Originator Exelixis Inc Licensee Bristol-Myers Squibb Co Status Phase III Clinical Indications Cancer, Glioblastoma, NSCLC, Pancreas tumor, Thyroid tumor Actions Anticancer protein kinase inhibitor, FLT3 tyrosine kinase inhibitor, Hepatocyte growth factor antagonist, KIT tyrosine kinase inhibitor, MET tyrosine kinase receptor family inhibitor, RET tyrosine kinase receptor family inhibitor, Tek tyrosine kinase receptor inhibitor, VEGF-2 receptor antagonist Technologies Oral formulation, Small-molecule therapeutic Synonym BMS-907351 develops as a sporadic tumor, while approximately 40% of cases are hereditary [1059455]. Mutations associated with activation of the RTK have been reported in approximately 30 to 50% of sporadic cases and in virtually all hereditary cases of MTC [1052955]. One of the most common mutations occurs in the rearranged during transfection (*RET*) gene. RET is activated by receptor dimerization, which is facilitated by RET binding to a complex formed through the binding of a ligand of the glial cell line-derived neurotrophic factor (GDNF) family to a GDNF family receptor. RET-mediated signaling regulates cell survival, cell growth, and cell differentiation and migration [1052949]. Furthermore, the activation of mutated RET is associated with a predisposition to cancers such as multiple endocrine neoplasia type 2 (A and B) and MTC [1052952].

Gliomas are extremely aggressive brain tumors, and the majority of glioma-related deaths arise from primary brain neoplasms [1052958]. In the US, approximately 18,000 individuals are diagnosed with a glioma each year. Despite the use of the most advanced standard treatment options available (ie, combinations of surgery, radiotherapy and chemotherapy), GBM, the most malignant form of glioma, is associated with an average life expectancy of only 14 months [1052958]. Both human gliomas and experimental gliomas in animal models express several growth factors and their corresponding RTKs. Among these RTKs, VEGFR-2 (or kinase insert domain receptor) and mesenchymal-epithelial transition factor (MET; also known as c-Met or hepatocyte growth factor receptor) are two important contributors to glioblastoma malignancy.

VEGFR-2, a member of the VEGFR family of RTKs, is activated by several ligands, the most important of which is VEGF-A (commonly referred to as VEGF) [1052944]. Activation of VEGFR-2 is one of the main drivers of tumor angiogenesis, making inhibition of the VEGF pathway one of the most promising targets for molecular cancer therapy [340243], [656382], [1059449]. Therapeutic strategies to inhibit signaling via VEGFR-2 and activation of the VEGF pathway include mAbs directed against VEGF or VEGFR-2 [1059449]. For example, bevacizumab, a humanized mAb against VEGF that has been tested in clinical trials for the treatment of several cancer types, has demonstrated varying levels of efficacy [1059449]. Vandetanib (AstraZeneca plc; in phase III clinical development), an orally bioavailable multikinase inhibitor that targets VEGFR, EGFR and RET, has also displayed promising effects in some cancers, including NSCLC [1059450]. VEGFR-2 is overactivated in the majority of GBMs, mainly via the overexpression of VEGF [1059456]. Overexpression of VEGF correlates with tumor vessel density and poor patient prognosis, while inhibition of VEGF attenuates brain tumor growth in animal models [340243].

MET is also overexpressed in many cancers. Activation of MET, occuring via the only known ligand of the kinase, hepatocyte growth factor (HGF), has been associated with negative clinical outcomes in a variety of cancer types, including glioblastoma [1052930], [1052931], [1052934]. MET activation enhances malignancy by inducing tumor cell proliferation, survival, migration and invasion, and by promoting one of the hallmarks of cancer, angiogenesis [1052930], [1052937], [1052938]. Overexpression of MET occurs in a

subset of GBM cases, and *MET* amplification has been detected in 4% of human GBMs [1052969]. Additionally, MET can be activated in an autocrine manner by HGF, which has also been observed to be overexpressed in a subset of GBM [1052931]. Inhibition of MET and/or HGF in animal models of GBM leads to impairment of tumor growth [1052940], [1052942].

Lung cancer is one of the leading causes of cancer-related mortality worldwide [1052971]. NSCLC accounts for 80 to 85% of cases, with the majority of patients presenting with advanced disease at the time of diagnosis [1059460]. Patients with advanced disease have a median survival of approximately 10 months when treated with traditional platinum-based therapy [1052971]. Following the realization that EGFR may play a role in NSCLC, inhibitors of EGFR (such as gefitinib and erlotinib) have been clinically tested against the disease [1059457]. Furthermore, numerous preclinical studies have demonstrated that deregulation of VEGFR-2 and MET significantly contributes to NSCLC malignancy [1052976], [1052977]. VEGF expression significantly correlates with new vessel formation and inversely correlates with disease-free and overall survival in patients with NSCLC [1059458]. In addition, MET is expressed and phosphorylated in virtually all NSCLC tumors in humans [1052978], [1052979]. MET and HGF levels correlate with prognostic parameters and poor survival, while patients with metastatic disease exhibit higher MET expression at metastatic sites and higher plasma MET levels [1059459]. Furthermore, *MET* amplification in patients with NSCLC has been identified as one of the mechanisms of acquired resistance to therapies targeting EGFR [798072].

XL-184 (BMS-907351), in development by Exelixis Inc and Bristol-Myers Squibb Co (BMS), is a pan-tyrosine kinase inhibitor that is being evaluated for the potential oral treatment of cancer [979623]. The principal targets of XL-184 are MET, VEGFR-2 and RET [979623], making the drug an ideal candidate for treating cancers such as MTC, GBM and NSCLC. Preclinical studies have also highlighted that XL-184 may have potential for the treatment of various other types of cancer, in particular pancreatic carcinoma [1058452] and breast and colon cancer [979623]. Indeed, XL-184 has also been reported to inhibit RTKs that have less well-defined roles in cancer, including FMS-like tyrosine kinase 3 (FLT3), mast/stem cell growth factor receptor (KIT or c-Kit) and endothelial-specific receptor tyrosine kinase (TEK; also known as Tie2) [607256]. FLT3 plays a role in hematopoietic cell survival and proliferation, and is frequently mutated in patients with acute myeloid leukemia [841873]. KIT regulates cell proliferation, and *KIT* gain-of-function mutations have been identified in several cancers, including acute myeloid leukemia and gastrointestinal stromal tumors [1059452]. TEK, however, does not have a clearly established role in cancer [1059453].

At the time of publication, preclinical data for XL-184 and the results of a phase I clinical trial in patients with advanced solid malignancies as well as a phase II trial in patients with GBM had been disclosed. This drug profile reviews the development of XL-184. Notably, all of the data reported for the drug have been available only from conference abstracts and press releases.

Synthesis and SAR

At the time of publication, no information regarding the synthesis and SAR of XL-184 was available.

Preclinical development

The preclinical activity of XL-184 as a single agent or in combination with gefitinib was assessed [952011]. Cells from the gefitinib-sensitive EGFR mutant ($Glu^{746}Ala^{750}X$) human

NSCLC cell line HCC827 were cultured in increasing concentrations of gefitinib to generate the gefitinib-resistant cell line HCC827GR6, which displays high MET expression. The proliferation of HCC827 cells was dose-dependently suppressed by gefitinib (IC_{50} = 0.01 μM), and the combination of gefitinib and XL-184 did not alter this sensitivity. In contrast, the proliferation of HCC827GR6 cells was not suppressed by gefitinib (IC_{50} > 10 μM) and was only weakly suppressed by XL-184 (IC_{50} ~ 3 μM); however, the combination of gefitinib and XL-184 (in equimolar concentrations) resulted in potent inhibitory activity (> 50% inhibition with 0.01 μM of each agent). Western blot analysis of HCC827GR6 cells treated with gefitinib (1 μM), XL-184 (0.1 μM) or the combination (at the same doses as single-agent treatment) demonstrated that the drug combination inhibited relevant signaling pathways, as indicated by a reduced expression of the phosphorylated forms of EGFR, MET, HER3 (erythroblastic leukemia oncogene homolog 3; ErbB-3), AKT and ERK1/2 [952011].

In HCC827GC6 xenograft tumors established in female nude mice, single-agent erlotinib (100 mg/kg po, single dose) inhibited tumor growth weakly, while single-agent XL-184 (10 mg/kg po, single dose) elicited slightly greater inhibition of tumor growth. In contrast to both single-agent treatments, the combination of XL-184 and erlotinib caused tumor regression in all animals. Using the same model at the same doses, western blot analysis of tumor lysates (prepared 4 h after drug administration) indicated that the combination of XL-184 and erlotinib inhibited the phosphorylation of AKT [952011].

The impact of XL-184 on MET phosphorylation was investigated using the human NSCLC adenocarcinoma cell line H441, which contains wild-type EGFR and active, overexpressed wild-type MET [952011]. Following the establishment of H441 NSCLC tumors in female nude mice, XL-184 (3, 10, 30 or 100 mg/kg po, single dose) was administered. Western blot analysis of tumor lysates (prepared 4 h after drug administration) demonstrated that XL-184 inhibited MET phosphorylation and was associated with a dose-dependent regression of xenograft tumors [952011].

Another study was conducted in 14-week-old RIP-Tag2 transgenic mice, a model of pancreatic carcinoma [1058452]. Treatment with XL-184 resulted in smaller tumors after 3 weeks ($p < 0.05$) compared with the use of either vehicle or an anti-mouse VEGF antibody. Tumors treated with XL-184 were also less invasive (invasion index 4.5; $p < 0.05$) than those treated with vehicle (invasion index 12.7) or antibody (invasion index 18.9), for which liver metastases were more numerous. Only animals treated with XL-184 survived to 20 weeks of age [1058452].

Several press releases have reported that XL-184 has potent inhibitory activity against VEGFR-2, MET, RET, KIT, TEK and FLT3 in a variety of human tumor cell lines and xenograft models, including breast, colon, brain, lung and thyroid cancers [607256] [928783] [979623].

Toxicity

At the time of publication, detailed data regarding the toxicity of XL-184 in animals were not available. However, one report had stated that XL-184 (0.8-mg/kg) was severely toxic in mice [741136].

Metabolism and pharmacokinetics

At the time of publication, little data regarding the metabolism and pharmacokinetics of XL-184 in animals were available. A press release from Exelixis stated that XL-184 displayed significant oral bioavailability and an excellent pharmacokinetic profile, details of

which were disclosed in an IND application submitted to the US FDA [607256]. Additionally, in whole-brain lysates of non-tumor-bearing mice, XL-184 attained 20% of peak plasma levels, indicating the ability of the drug to penetrate the blood-brain barrier [1009977].

A phase I clinical trial (ClinicalTrials.gov identifier: NCT00215605) assessed the pharmacokinetics of XL-184 following intermittent (escalating doses at 0.08 to 11.52 mg/kg po [powder formulation], qd for 5 days followed by a 9-day washout) and daily (175 or 265 mg po [powder formulation], qd, or 175 or 250 mg po [capsule formulation], qd) dosing in patients with advanced solid malignancies [741136], [843102], [912013], [951540], [1051828], [1052332]. All patients were instructed to fast for 2 h before and 1 h after drug administration [741136], [951540]. XL-184 displayed a linear pharmacokinetic profile [741136], [843102], [912013], [951540], [1052332]. Systemic drug exposure and peak plasma levels increased dose-dependently [741136], [951540], with average C_{max} values of 34, 70, 198, 322 and 603 ng/ml following the fifth dose of XL-184 at 0.08, 0.16, 0.32, 0.64 and 1.28 mg/kg, respectively [1052332]. The terminal $t_{1/2}$ value was ~ 100 h and did not appear to be influenced by either dose level or treatment duration [741136], [843102], [912013], [951540], [1051828]. A $t_{1/2}$ value of 80 to 90 h was associated with drug concentrations of > 200 ng/ml, levels that were maintained for 96 h after the fifth dose of 1.28 mg/kg of XL-184 [1052332]. XL-184 was orally bioavailable and quickly absorbed, with a dose of 175 mg resulting in a T_{max} value of 5 h on day 1 [951540]. Plasma concentrations of XL-184 reached steady-state levels by day 15, and a drug accumulation ratio of approximately 4- to 6-fold was observed with daily dosing [951540].

A phase II clinical trial (NCT00704288) in patients with progressive GBM in first or second relapse suggested that the pharmacokinetics of XL-184 (175 mg po, qd) were consistent with those observed in the NCT00215605 phase I trial. On day 15, average drug exposure was 1700 and 1950 ng/ml pre- and post-dose, respectively, with a C_{max} value of 2310 ng/ml [1009977].

Clinical development

Phase I

A phase I, non-randomized, open-label, uncontrolled, single-group, first-in-human, dose-finding clinical trial (NCT00215605; XL184-001) evaluated intermittent (escalating doses at 0.08 to 11.52 mg/kg po [powder formulation], qd for 5 days followed by a 9-day washout) and daily (175 or 265 mg po [powder formulation], qd, or 175 or 250 mg po [capsule formulation], qd) dosing schedules of XL-184 in patients (total n = 85) with advanced solid malignancies [741136], [843102], [912013], [951540], [1051828], [1052332]. Patients were instructed to fast for 2 h before and for 1 h after drug administration; dose-escalation proceeded in cohorts of three to six patients, and doses were escalated by 100% unless a drug-related adverse events (AE) of grade 2 or higher was reported or the MTD was determined [741136], [951540]. The trial incorporated a standard 3 + 3 design [951540], [1051828], but included an expansion cohort at the MTD for patients with MTC that was metastatic and/or locally advanced or recurrent and not appropriate for resection [912013], [951540], [1051828]. Imaging was performed at baseline and on day 28, and then every 8 weeks thereafter; tumor measurements were based on RECIST criteria [741136], [843102], [912013], [951540], [1051828], [1052332].

Preliminary results for this clinical trial indicated that the MTD of XL-184 was 175 mg once daily [1051828]. In patients with MTC (n = 34) and measurable disease in the expanded MTD cohort, 41% had a partial response (26% confirmed), and the disease control rate (partial response plus stable disease for > 3 months) was 84% [1051828]. A more detailed

preliminary analysis, using data from an earlier time point in the trial, was also reported [951540]. Of the evaluable patients (≥ 3 months of follow-up; n = 70), a confirmed partial response was experienced by 7 patients (all with MTC; two of the seven responses had been sustained for > 17 months), an unconfirmed partial response was experienced by 6 patients (MTC, n = 5; neuroendocrine tumor, n = 1) and stable disease was observed in 28 patients with a variety of tumor types, including papillary and follicular thyroid carcinoma (papillary and follicular thyroid carcinoma, n = 1 each; MTC, n = 9); progressive disease was experienced by 39 patients. In patients with MTC who received the MTD (n = 7), significant increases in levels of placental growth factor and VEGF, and a significant decrease in soluble VEGFR-2, were observed; additionally, an increase in soluble MET levels was also observed in four out of seven patients with MTC. The best overall response rate (partial plus complete responses) in patients with MTC was 55% (12 out of 22 patients), and the median time-to-progression had not been reached (with ≥ 3 months follow-up) [951540]. Although most of the patients with MTC exhibited reductions in plasma calcitonin and carcinoembryonic antigen [912013], [951540], [1051828], no relationship between the magnitude of the reduction in levels of these biomarkers and the magnitude of maximum tumor reduction was identified [951540]. Responses to XL-184 did not appear to be dependent on the RET status of individual patients [951540], [1051828]. All subsequent clinical trials of XL-184 used the capsule formulation.

At the time of publication, a phase I, dose-finding, non-randomized, open-label, parallel-group clinical trial (NCT00960492; XL184-002) evaluating XL-184 (25 and 100 mg po, qd) in combination with temozolomide and radiotherapy (first-line treatment) was recruiting patients (expected n = 85) with grade 4 astrocytic tumor (including glioblastoma, giant cell glioblastoma, gliosarcoma and glioblastoma with oligodendroglial components). The primary endpoints were the safety and tolerability of XL-184 in combination with first-line therapy during the concurrent, rest and maintenance phases of treatment. Secondary endpoints were to evaluate the plasma pharmacokinetics and pharmacodynamics of XL-184 as a single agent or in combination with first-line therapy. Trial completion was expected in December 2010.

At the time of publication, a phase I/II, randomized, open-label, parallel-group clinical trial (NCT00596648; XL184-202) of XL-184 (po, qd), either alone or in combination with erlotinib, was recruiting patients (expected n = 86) with NSCLC who had progressed after demonstrating initial benefit from erlotinib. Primary endpoints for both phases of the trial were the pharmacokinetics and pharmacodynamics of each agent alone or in combination. The phase-specific primary endpoints were the safety, tolerability and MTD of XL-184 in combination with erlotnib (the phase I portion of the trial), and to estimate the objective response rate of XL-184 alone or with erlotinib in patients who had progressed after responding (stable disease for > 6 months) to erlotinib (phase II). The secondary endpoints for the phase I portion of the trial were response rate, progression-free survival, duration of response and overall survival following treatment with XL-184 alone or in combination with erlotinib. For phase II, secondary endpoints included the long-term safety and tolerability of XL-184 and the progression-free survival, duration of response and overall survival following treatment with the drug alone or in combination with erlotinib. Completion of this trial was expected in December 2009.

Finally, a phase I, open-label, single-group assignment, ascending-dose clinical trial (NCT01018745; CA205-001) of XL-184 (75, 125 and 175 mg po, qd) in Japanese patients (expected n = 20) with advanced or metastatic solid tumors was planned to begin in January 2010. The primary endpoint was to establish the MTD of XL-184, and secondary endpoints would assess the safety, pharmacokinetics and pharmacodynamics of the drug. Trial completion was expected in September 2011.

Phase II

A phase II, open-label, uncontrolled, single-group clinical trial (NCT00704288; XL184-201) evaluated single-agent XL-184 (175 mg po, qd) in patients (n = 46) with progressive or recurrent GBM in first or second relapse [1009977], [1009978], [1009979], [1055216]. Analyses conducted by an independent radiology facility (IRF) reported that a confirmed partial response was experienced by 8 and 21% of patients who were antiangiogenic treatment-experienced and -naïve, respectively. The median duration of response (across the entire patient cohort) was 5.9 months, and the median IRF-determined progression-free survival (estimated using the Kaplan-Meier method) was 111 days. An independent review of scans obtained from patients whose disease had progressed (n = 28) revealed that 3 out of 22 patients with a local pattern of recurrence at baseline had a diffuse progression pattern following treatment; the pattern of progression was unaltered in all patients who presented with diffuse (n = 4) or multifocal (n = 2) disease [1055216].

An earlier presentation of results from the same clinical trial indicated that, out of 14 patients who were receiving corticosteroids at baseline, 5 were able to reduce their steroid requirement by ≥ 50% [1009977]. In patients (n = 25, of whom 20 were antiangiogenic treatment-naïve) who underwent imaging assessments (post-contrast T1-based measurements and fluid-attenuated inversion recovery images) on day 28, reductions in tumor volume of up to 50% were observed [1009978]. At day 28, levels of mobile lipids were reduced and levels of major metabolites were increased compared with on day 1, suggesting a reduction in the tumor necrotic core and improvement of mass effect [1009978]. A preliminary examination of plasma biomarkers or tumor tissue biomarkers revealed no relevant findings with regard to predicting a response to XL-184 treatment [1009979].

Because of the high frequency of dose reductions and interruptions (see *Side effects and contraindications* section), the clinical trial protocol was amended to allow a lower starting dose of XL-184 (125 mg po, qd), with the expectation that more consistent drug exposure would translate into improved tolerability and efficacy [1009977]. A more recent report confirmed that 38 patients had been enrolled in the 125-mg dose group and 18 had at least one IRF-read post-baseline scan [1055216]. Among this group, 2 patients, neither of whom had received prior antiangiogenic therapy, experienced a confirmed partial response, and out 8 of 14 patients, all of whom were antiangiogenic therapy-naïve, achieved ≥ 50% reductions in enhancing lesions per IRF. At the time of publication, enrollment in the 175-mg dose group had been completed [1055216], while patients continued to be recruited in the 125-mg dose group (total expected n = 106); trial completion was expected in December 2011.

A phase II, randomized, double-blind, parallel-group, discontinuation clinical trial (NCT00940225; XL184-203) was enrolling patients (expected n = 600) with advanced solid tumors. All patients were to receive open-label XL-184 (100 mg po, qd) for 12 weeks. After 12 weeks of treatment, patients with a partial or complete response were to continue receiving XL-184 until disease progression, and patients with stable disease were to be randomized to either XL-184 or placebo until disease progression. The primary endpoint was to evaluate the efficacy of XL-184 using MRI, CT and/or bone scans every 6 weeks. Secondary endpoints would assess the safety and tolerability, as well as the correlation between the pathway dysfunction of disease-related genes or proteins (eg, MET) and downstream signaling molecules with clinical outcome, and would further characterize the pharmacokinetics and pharmacodynamics of XL-184. Trial completion was expected in July 2011.

Phase III

In June 2008, following a Special Protocol Assessment, the FDA and Exelixis reached an agreement on the design of a phase III clinical trial to support the registration of XL-184 [917116]. The phase III, randomized, double-blind, placebo-controlled, parallel-group, international trial (NCT00704730; XL184-301) was to assign patients (expected n = 315) with unresectable, locally advanced or metastatic MTC in a 2:1 ratio to XL-184 (po, qd) or placebo. The primary endpoint was progression-free survival, and secondary endpoints were overall survival, objective response rate and the duration of response in patients with measurable disease, as well as the safety, tolerability, pharmacokinetic and pharmacodynamic effects of XL-184. At the time of publication, the trial was recruiting patients and trial completion was expected in March 2013.

Side effects and contraindications

In the phase I clinical trial for XL-184 in patients with advanced malignancies (NCT00215605), no grade 4 toxicities were observed [951540]. In preliminary safety data from 71 patients, a total of eight DLTs, seven of grade 3 severity, were reported by 6 out of 71 assessable patients. Of these DLTs, one case of each of palmar/plantar erythema (PPE), AST, ALT and lipase elevations occurred in the 11.52-mg/kg cohort, two cases of mucositis (one of which was grade 2) and one case of AST elevation occurred in the 265-mg/day (powder formulation) cohort and one case of PPE occurred in the 250-mg/day (capsule formulation) cohort [951540]. Serious AEs were reported by 38 patients, with seven of these events (experienced by 6 patients) classified as treatment-related: grade 4 pulmonary hypertension; grade 3 nausea, skin infection, hypothyroidism and hyperbilirubinemia; and grade 2 ileus and diverticulitis [951540]. Common AEs (all < grade 3) included diarrhea (24%), nausea and vomiting (18% and 10%, respectively), fatigue (15%), anorexia (13%), mucositis (13%), transaminitis (11%) and hypertension (10%) [951540].

The phase II clinical trial in patients with GBM (NCT00704288) was discontinued by 41 out of 46 patients in the 175-mg dose group, with eight discontinuations occurring because of an AE [1055216]. At least one XL-184-related serious AE was reported by 13 out of 46 patients. Severe (≥ grade 3) side effects that were reported by ≥ 5% of patients were fatigue (35%), headache (11%), PPE (9%), confusional state (9%), ALT elevation (9%), convulsion (9%), lymphopenia (9%), hypophosphatemia (9%), lipase elevation (9%), diarrhea (7%), AST elevation (7%) and gait disturbance (7%). AEs (of any grade) that occurred in this trial and are commonly associated with VEGF inhibition included hypertension (37%), hemorrhage (28%), proteinuria (28%), thromboembolic event (7%), craniotomy wound dehiscence (4%) and perirectal abscess (2%). Overall, AEs resulted in 89% of patients requiring treatment interruption for a median time of 18 days, and 43% of patients required a single dose reduction. The median actual/planned dose ratio was 65%, corresponding to a median daily dose of 114 mg [1055216].

Preliminary safety data from the 125-mg dose cohort suggested that the pattern of dose reductions and interruptions was similar to that observed with the 175-mg dose [1055216]; specifically, 14 out of 18 and 6 out of 18 patients had a dose interruption and a dose reduction, respectively [1051767]. The most common reported non-serious AEs that led to a dose reduction or interruption included fatigue, PPE, transaminase elevation, lipase and amylase elevation, and mucositis [1051767], [1055216]. At least one XL-184-related serious AE was reported by 6 out of 38 patients: one patient each experienced ischemic cerebral infarction, deep vein thrombosis, hemorrhage and dehydration; one patient experienced four events simultaneously (amylase elevation, thrombocytopenia, neutropenia and lipase elevation); and another patient experienced a pulmonary embolism that occurred simultaneously with deep vein thrombosis [1055216]. At the time of publication, evaluation

at the 125-mg dose level was to continue and AEs were to be managed proactively, with the aim of allowing dose reduction, rather than interruption [1051767], [1055216].

Patent summary

Although the structure of XL-184 had not been disclosed at the time of publication, reported activity as an inhibitor of several tyrosine kinases suggests that the drug may be covered by WO-2005030140 from Exelixis. The WO-2005030140 application claims substituted quinoline and quinazoline compounds for modulating kinase receptors, particularly MET, VEGFR-2, KIT, FLT3 and FLT4. Potent inhibitors of kinase activity are claimed for the prevention and treatment of aberrant cellular activity, for screening for modulators of RTK activity, and for the treatment of a variety of proliferative and inflammatory disorders.

No new compounds are claimed in WO-2005030140; however, the granted US equivalent, US-07579473, which is due to expire in September 2024, contains claims for novel compounds, including three specified compounds. The preferred of the three compounds is *N*-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-*N*'-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide (claim 5), which may be XL-184. The same compound is also the most preferred in US-20090170896, another pending US equivalent of WO-2005030140, claiming the use of the compounds for treating various cancers, particularly glioma and glioblastoma, further supporting the possibility that the preferred compound is XL-184. In addition, the preferred compound in claim 5 of US-07579473 corresponds to compound 12 in claim 105 of WO-2005030140, where the preferred compound is claimed for use along with more than 100 additional specific compounds, including foretinib (GlaxoSmithKline plc [GSK]/Exelixis Inc; phase II [861071]) (compound 5, claim 10), which was derived from the same research alliance as for XL-184 [955311]. The compounds disclosed in WO-2005030140 are structurally similar to quinoline and quinazoline compounds claimed by Kirin Brewery Co Ltd in WO-09717329 and several subsequent applications. This similarity may explain why the compounds in WO-2005030140 are not claimed *per se*.

With the exception of WO-2005030140, Exelixis has two other patent applications that potentially relate to XL-184. WO-2006014325 claims 5,6-fused bicyclic compounds for modulating kinase activity, particularly MET, VEGFR-2 and FLT3 activity, and WO-2006108059 claims novel quinoline compounds and their use for modulating MET, VEGFR-2, KIT, FLT3 and FLT4 activity. The WO-2006108059 application specifically claims one compound, *N*-[3-fluoro-4-({6-(methyloxy)-7-[(3-morpholin-4-ylpropyl) oxy]quinolin-4-yl}oxy)phenyl]-*N*'-[2-(4-fluorophenyl) ethyl]ethanediamide; this compound, a close analog of foretinib, could potentially be XL-184. WO-2006108059 is based on a priority filing made on April 6, 2005 – 1 day prior to the publication of WO-2005030140.

Current opinion

The aberrant activation of RTKs occurs in most human cancers. This activation has been demonstrated to contribute to malignancy by inducing tumor cell proliferation, survival, invasion and migration, and by enhancing tumor angiogenesis. Based on this evidences, numerous RTK inhibitors with varying specificities have been investigated and/or approved for cancer therapy. Although the use of these agents has yielded promising antitumor effects in cells and animal models of cancer, the majority of RTK inhibitors have not produced a significant impact on disease in clinical trials. The relative failure of available cancer treatments can be attributed to various possible reasons. In addition to the well-documented heterogeneity of human cancers and their dependency on multiple molecular pathways, RTK signaling redundancy and compensatory mechanisms are believed to hinder the success of RTK inhibitors in the clinic [1052984]. A plethora of literature has demonstrated that multiple RTKs are coactivated in cancer and that redundant inputs drive and maintain

downstream signaling. Therefore, single RTK inhibition might be predicted to fail to inhibit tumor growth significantly, in contrast to the combined targeting of multiple RTKs. The concept of multiple RTK inhibition has been demonstrated *in vitro* using glioblastoma cells and in animal models [1052984]. In glioblastoma cells, combinations of RTK inhibitors and/or RNAi, but not single agents, reduced various measures of malignancy [1052984]. Additionally, cancer cells have been demonstrated to compensate for single RTK inhibition by activating other RTKs via various mechanisms, including gene amplification. For example, lung cancers with activating mutations in the EGFR develop resistance to tyrosine kinase inhibitors by recruiting the MET receptor kinase to activate HER3 and the PI3K/Akt cell survival pathway [798072], thus providing a rationale for the combination targeting of RTKs. By targeting multiple RTKS that are known to contribute to malignancy, XL-184 provides a theoretical therapeutic advantage compared with more specific RTK inhibitors. Because XL-184 does not target EGFR, which is a major RTK driver of malignancy in many cancers, including GBM and NSCLC, combination therapies with EGFR inhibitors might provide an additional therapeutic advantage. This theory is also supported by the preclinical study that demonstrated resensitization of cells resistant to the EGFR inhibitors gefitinib and erlotinib by XL-184 [952011].

Because VEGF is one of the most highly and frequently overexpressed molecules in glioblastoma, angiogenesis is a particular problem for this type of cancer. VEGF pathway inhibitors have been approved by the FDA, and their use has had promising therapeutic effects; however, data from animal studies suggests that angiogenesis inhibition may promote an invasive phenotype in glioblastoma tumor cells [1052985], represent a potentially important mechanism of resistance to antiangiogenic therapies. Combination therapy with antiangiogenic and anti-invasion agents in glioblastoma is therefore a promising approach that may produce synergistic antitumor effects and a survival benefit for patients with these tumors. Given that MET is also known to promote tumor cell invasion in glioblastoma cells and animal models, this activity may provide an additional rationale for the simultaneous targeting of VEGFR-2 and MET and could represent another theoretical advantage for the use of agents that can inhibit both pathways, such as XL-184.

In summary, XL-184 is a promising new inhibitor of multiple RTKs that has conceptual therapeutic advantages compared with more specific RTK inhibitors. XL-184 has exhibited good oral availability and pharmacokinetic properties, combined with relatively low toxicity and promising therapeutic effects in the first clinical trials; thus, such encouraging evidence provides support for the further testing and analysis of this drug.

Deals

GlaxoSmithKline plc

In October 2002, Exelixis and GSK signed an agreement to discover and develop novel therapeutics in the areas of vascular biology, inflammatory disease and oncology [468115], [468117]. In an amendment to the collaboration in January 2005, GSK had an option to develop and commercialize up to three drugs from Exelixis, including XL-184 [579117]. In October 2008, however, GSK elected not to exercise its option to license XL-184. Exelixis agreed to pay GSK a 3% royalty on any future XL-184 product [955311].

Bristol-Myers Squibb Co

In December 2008, BMS licensed exclusive worldwide rights to XL-184, as well as the compound XL-281, from Exelixis. BMS would make an upfront payment of US $195 million, plus additional payments totaling US $45 million during 2009. The companies wouldcodevelop XL-184, with Exelixis being granted an option to US copromotion rights. Costs and profits would be shared in the US. Exelixis would be responsible for clinical

development until 2010. Exelixis would receive sales-based milestones of up to US $150 million and double-digit royalties on ex-US sales; however, should Exelixis opt-out of codevelopment, the company would receive developmental and regulatory milestones of up to US $295 million, and double-digit royalties on worldwide sales [979623]. This deal had been approved by January 2009, and Exelixis had received an upfront cash payment of US $195 million [990277].

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Therapeutic XL-184

Originator Exelixis Inc

Licensee Bristol-Myers Squibb Co

Status Phase III Clinical

Indications Cancer, Glioblastoma, NSCLC, Pancreas tumor, Thyroid tumor

Actions Anticancer protein kinase inhibitor, FLT3 tyrosine kinase inhibitor, Hepatocyte growth factor antagonist, KIT tyrosine kinase inhibitor, MET tyrosine kinase receptor family inhibitor, RET tyrosine kinase receptor family inhibitor, Tek tyrosine kinase receptor inhibitor, VEGF-2 receptor antagonist

Technologies Oral formulation, Small-molecule therapeutic Synonym BMS-907351

Development status

Developer	Country	Status	Indication	Date	Reference
Bristol-Myers Squibb Co	Europe	Phase III	Thyroid tumor	15-JAN-09	990277
Bristol-Myers Squibb Co	World	Phase III	Thyroid tumor	15-JAN-09	990277
Bristol-Myers Squibb Co	US	Phase III	Thyroid tumor	15-JAN-09	990277
Exelixis Inc	Europe	Phase III	Thyroid tumor	23-JUN-08	921314
Exelixis Inc	World	Phase III	Thyroid tumor	23-JUN-08	921314
Exelixis Inc	US	Phase III	Thyroid tumor	23-JUN-08	921314
Bristol-Myers Squibb Co	US	Phase II	Cancer	31-JUL-09	1030055
Exelixis Inc	US	Phase II	Cancer	31-JUL-09	1030055
Bristol-Myers Squibb Co	US	Phase II	Glioblastoma	15-JAN-09	990277
Exelixis Inc	US	Phase II	Glioblastoma	31-MAY-08	921619
Bristol-Myers Squibb Co	US	Phase II	NSCLC	15-JAN-09	990277
Exelixis Inc	US	Phase II	NSCLC	07-JAN-08	865302
Exelixis Inc	US	Discovery	Pancreas tumor	16-NOV-09	1058452