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REGORAFENIB

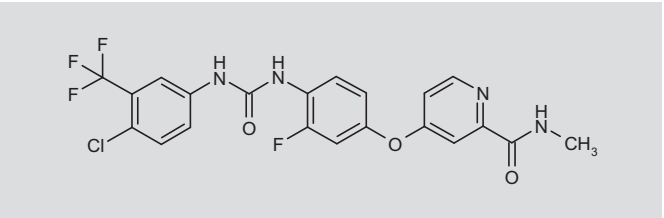
Rec INN

Broad-Spectrum Kinase Inhibitor
Oncolytic

BAY-73-4506

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

InChI: 1S/C21H15ClF4N4O3/c1-27-19(31)18-10-13(6-7-28-18)33-12-3-5-17(16(23)9-12)30-20(32)29-11-2-4-15(22)14(8-11)21(24,25)26/h2-10H,1H3,(H,27,31)(H2,29,30,32)



$C_{21}H_{15}ClF_4N_4O_3$

Mol wt: 482.815

CAS: 755037-03-7

EN: 395674

SUMMARY

Regorafenib is an orally active inhibitor of VEGFR-2 and -3, c-Kit, TIE-2, PDGF-R-β, FGFR-1, Ret, c-RAF and MAP kinase p38. Preclinical in vitro and in vivo studies demonstrate a broad spectrum of activity, likely due to the targeting of several angiogenic, stromal and oncogenic kinases. In early phase I and II studies, regorafenib has been shown to be well tolerated and demonstrated notable antitumor activity. Regorafenib is currently undergoing extensive clinical development in patients with advanced renal cell cancer, colorectal cancer, non-small cell lung cancer, hepatocellular carcinoma and gastrointestinal stromal tumors.

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SYNTHESIS*

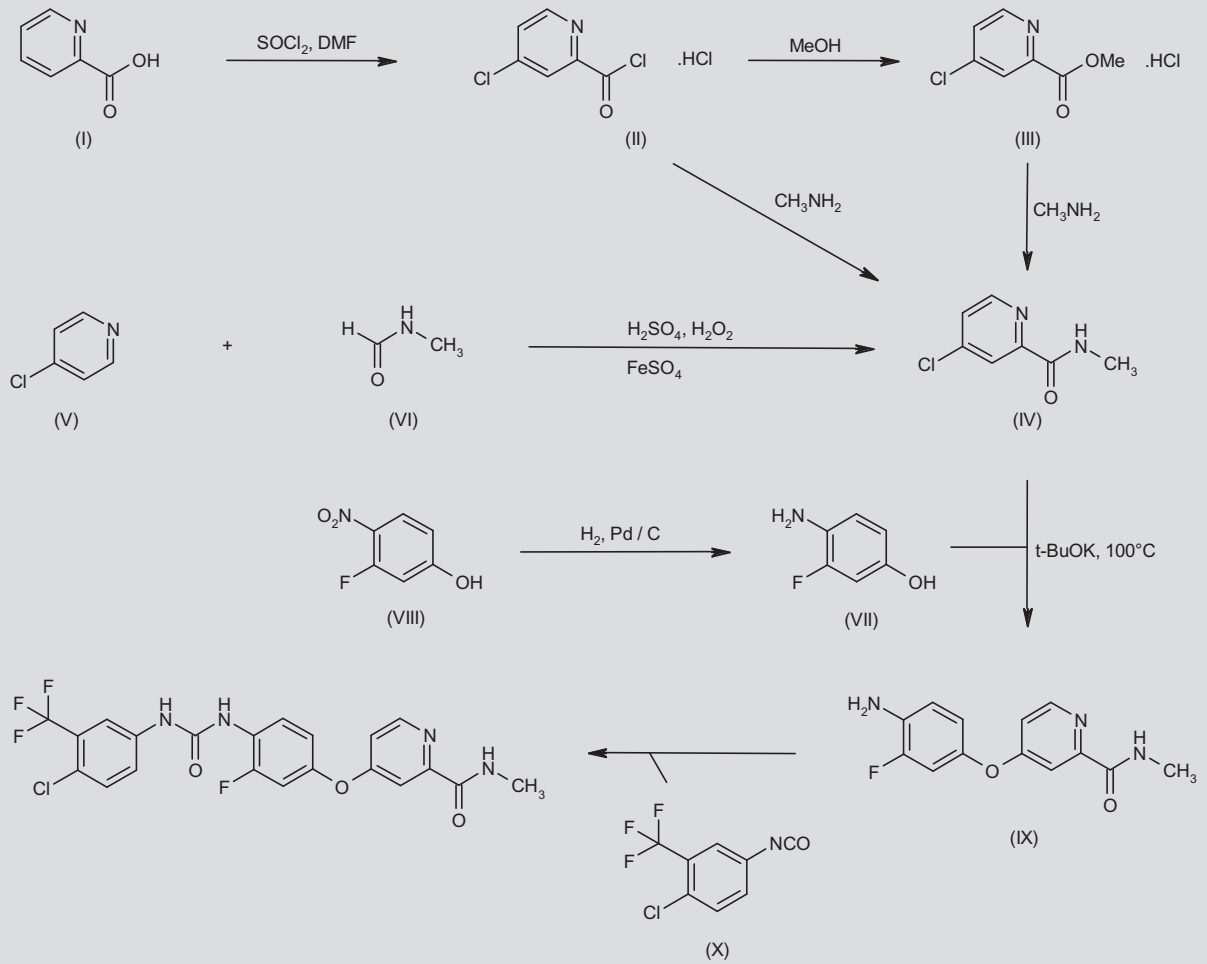
Chlorination of picolinic acid (I) with $SOCl_2$ in the presence of DMF at 72 °C gives 4-chloropyridine-2-carbonyl chloride hydrochloride (II), which is then esterified with MeOH to afford the corresponding methyl ester (III). Aminolysis of ester (III) with methylamine in MeOH gives 4-chloro-*N*-methylpyridine-2-carboxamide (IV) (1), which can also be prepared by direct amidation of acid chloride (II) with methylamine in THF/MeOH (1, 2) or by Minisci reaction of 4-chloropyridine (V) with *N*-methylformamide (VI) in the presence of H_2SO_4, H_2O_2 and $FeSO_4·7H_2O$ (1). Condensation of chloropicolinamide (IV) with 4-amino-3-fluorophenol (VII) –prepared by reduction of 3-fluoro-4-nitrophenol (VIII) by means of H_2 and Pd/C in EtOAc– in the presence of *t*-BuOK in DMAc at 100 °C provides the 4-phenoxypyridine derivative (IX), which is finally coupled with 1-chloro-4-isocyanato-2-(trifluoromethyl)benzene (X) in toluene (3). Scheme 1.

BACKGROUND

In 2001, the U.S. Food and Drug Administration (FDA) approved imatinib for the treatment of patients with metastatic gastrointestinal stromal tumor (GIST) (4). Since then, a large number of new kinase inhibitors have been studied in the field of solid tumor oncology. Many of these agents have been approved by the FDA and the European Medicines Agency (EMEA) for a variety of indications, including GIST, renal cell cancer (RCC), hepatocellular carcinoma (HCC) and non-small cell lung cancer (NSCLC). These drugs are not only challenging the way in which anticancer treatments have been traditionally developed, administered and evaluated for efficacy, but are also shedding light on the genomic heterogeneity of cancer, even within a given disease entity (5).

Regorafenib (formerly known as BAY-73-4506) is a novel, orally active, diphenylurea multikinase inhibitor, the antitumor activity of which is mediated by the inhibition of vascular endothelial growth factor receptor VEGFR-2 and -3, tyrosine-protein kinase receptor TIE-2, platelet-derived growth factor receptor PDGF-R-β, proto-

Scheme 1. Synthesis of Regorafenib



oncogene c-Kit, basic fibroblast growth factor receptor FGFR-1, tyrosine-protein kinase receptor Ret, proto-oncogene c-RAF and MAP kinase p38 (Table I). Regorafenib is structurally related to sorafenib (6), a broad-spectrum kinase inhibitor approved for the treatment of advanced HCC (7) and RCC (8). Despite the similar spectrum of kinase inhibition, in vitro biochemical assays showed that regorafenib is a more potent inhibitor of VEGFR-2, PDGF-R-β, FGFR-1 and c-Kit than sorafenib (6, 9). Moreover, the inhibition of TIE-2 confers regorafenib broader antiangiogenic properties than sorafenib.

Sorafenib and regorafenib also display the ability to interfere with the mitogen-activated protein (MAP) kinase intracellular signaling pathway, which is frequently aberrantly activated in human cancer (10). Both compounds target Raf (c-RAF), wild-type B-raf and B-raf^{V600}. However, the inhibition of MAP kinase p38 is a peculiar characteristic of regorafenib.

The extended spectrum of target kinases involved in angiogenesis and oncogenesis makes regorafenib a promising antitumor compound. In this monograph, we review the pharmacological, pharmacokinetic and pharmacodynamic features of regorafenib, along with preliminary data on its clinical antitumor activity.

Table I. *Biochemical activity of regorafenib: target inhibition*

Target inhibition (biochemical assay)	Regorafenib IC_{50} (nM) ± SD (n)
VEGFR-1	13 ± 0.4 (2)
Murine VEGFR-2	4.2 ± 1.6 (10)
Murine VEGFR-3	46 ± 10 (4)
TIE-2	311 ± 46 (4)
PDGF-R-β	22 ± 3 (2)
FGFR-1	202 ± 18 (6)
c-Kit	7 ± 2 (4)
Ret	1.5 ± 0.7 (2)
c-RAF	2.5 ± 0.6 (4)
B-raf	28 ± 10 (6)
B-raf^{V600E}	19 ± 6 (6)

PRECLINICAL PHARMACOLOGY

Since regorafenib is a relatively new kinase inhibitor, the available data on its chemistry, safety and activity consist mainly of reports in abstract form.

Wilhelm and colleagues recently presented the first manuscript summarizing preclinical data for regorafenib. Regorafenib demonstrated antiproliferative activity in a wide array of cell lines. The activity of regorafenib on tumor cell lines varied widely. Breast, pancreas and lung cancer cell lines were potently inhibited by regorafenib (IC_{50} = 2-5 nM), including GIST and thyroid cancer cell lines (IC_{50} = 30-40 nM), while HCC, colorectal cancer (CRC) and melanoma cell lines required higher concentrations for inhibition (IC_{50} = 500-3000 nM). Regorafenib was also tested in human umbilical vein endothelial cells (HUVEC) and human aortic smooth muscle cells (HAOSMC) given its antiangiogenic properties. Regorafenib inhibited the proliferation of HUVEC induced by vascular endothelial growth factor $VEGF_{165}$ and basic fibroblast growth factor (bFGF) with IC_{50} values of 3 and 127 nM, respectively, while PDGF-BB-induced proliferation of HAOSMC was inhibited with an IC_{50} of 146 nM (9).

In addition, regorafenib has demonstrated antitumor activity in vivo against a wide array of human tumor xenografts in mice (9). Regorafenib given at oral doses of 10-30 mg/kg effectively inhibited the growth of CRC, breast cancer (BC), RCC, lung, melanoma, pancreatic and ovarian cancer xenografts. In RCC and BC xenografts, treatment with regorafenib also led to dimensional responses. A reduction in phosphorylated extracellular signal-regulated kinase ERK-1/2 assessed by immunohistochemistry was seen in the BC xenograft, confirming that the drug efficiently inhibited the MAP kinase pathway.

Using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) with Gadomer-17, a new high-molecular-weight MRI contrast agent, important information on the pharmacodynamics of regorafenib was obtained (9). In a rat glioblastoma model treatment with 10 mg/kg of regorafenib significantly decreased the perfusion of the tumor and the extravasation of the contrast agent, as measured by $IAUC_{360}$, the area under the curve after the initial 360 s from the administration of the contrast agent. Interestingly, this effect was long-lasting, persisting for up to 2 days. In order to gain some insight into the mechanisms responsible for the changes observed in DCE-MRI, immunohistochemical staining for CD31, an endothelial cell marker, was carried out in BC and CRC xenografts. Compared to control animals, regorafenib induced a significant reduction in the microvessels within the tumor, which may account for the reduction in tumor blood flow seen on DCE-MRI.

SAFETY

The most common toxicities of regorafenib seen in preliminary phase I/II studies are summarized in Table II. Skin toxicity (hand–foot syndrome, rash, desquamation, alopecia), fatigue, hypertension, mucositis, diarrhea and thyroid dysfunction were observed for regorafenib, but structurally related compounds may cause similar adverse events (AEs). Sorafenib and sunitinib are among the closest drugs to regorafenib and specific guidelines for the prevention and treatment of AEs associated with them have been developed (11-16).

Most toxicities reported to date with regorafenib are grade 1/2. However, in the case of severe AEs and/or AEs resistant to therapy, dose modification, interruption and discontinuation may be required. Upon improvement or resolution of the AEs, the drug may be re-escalated or reintroduced.

The literature on the management of AEs associated with kinase inhibitors is rapidly expanding. Although no guidelines on regorafenib have been published yet, the recommendations developed for compounds with a similar kinase inhibitor profile may ultimately prove helpful in patients treated with regorafenib, although the clinical experience with regorafenib continues to expand.

CLINICAL STUDIES

The results of the first dose-escalation study of regorafenib in humans were reported by Frost and coworkers at the Annual Meeting of the American Society of Clinical Oncology in 2008 (8). Fifty-two patients with advanced solid tumors and progressive disease received oral regorafenib up to 220 mg on 21 days on/7 days off cycles. Colorectal cancer, ovarian cancer and malignant melanoma were among the most common diagnoses of patients enrolled in the study. Among the 33 patients evaluable for response, 9% achieved a partial response (PR) and 64% had stable disease (SD) after at least 7 weeks on study drug; 48% had SD or PR for > 11 weeks. The most common regorafenib-related AEs were hoarseness (54%), hand–foot syndrome and skin rash (50%; CTC grade 3 or 4: 13%), mucositis (35%), diarrhea (25%; CTC grade 3: 2%), hypertension (23%; CTC grade 3: 6%) and fatigue (23%; CTC grade 3: 2%). Hand–foot syndrome, diarrhea and thrombocytopenia were the main causes for dose reduction, treatment discontinuation or interruption in 15%, 8% and 6% of the cases, respectively. Pharmacokinetic analysis suggested that regorafenib displays a dose-dependent increase in exposure up to 160 mg, and then plateaus. The two active metabolites, M2 and M5, demonstrate a dose-dependent increase in exposure similar to the parent drug. Pharmacodynamic markers were also evaluated in this study. A decrease in soluble VEGFR-2 plasma levels and Gd-DTPA uptake at DCE-MRI correlated with drug exposure (17).

The results of an earlier phase I study were presented in 2007 (18). Twenty-two patients with advanced progressive disease, mainly CRC, RCC and pancreatic cancer, received oral regorafenib at doses of 10-120 mg/day given on a 21 days on/7 days off schedule. Interestingly, two patients with RCC and one patient with an osteosarcoma achieved a RECIST PR. Four patients had SD. Adverse events consisted of hoarseness (32%; all grade 1), hypertension (23%; all grade 1 or 2), fatigue (14%; one case of grade 3), hand–foot syndrome (14%; one case of grade 3) and mucositis (14%; all grade 1). Dose-limiting toxicities, identified at 120 mg daily, were fever, hand–foot syndrome, fatigue and leukopenia.

The pharmacokinetic/pharmacodynamic results of the study led by Frost et al. (17), in which the exposure to regorafenib showed a plateau at 160 mg administered 21 days on/7 days off, and the preliminary signs of activity on this schedule, led to the selection of this regimen for further development.

Table II. *Response rate and toxicity profile in the early phase I/II studies.*

Study (evaluable patients)	Patient characteristics	Disease control rate	Toxicity (≥ 20% of patients)
Shimizu, 2010 (N = 36)	Progressive, locally advanced or metastatic solid tumors Represented histologies included CRC, thyroid cancer, adenoid cystic tumor and head and neck tumor	67% (PR 6% + SD 61%)	Rash/desquamation 50% Hand–foot syndrome 32% Fatigue 32% Pain 29% Mucositis 24 Diarrhea 21%
Strumberg, 2009 (N = 38)	Progressive, locally advanced or metastatic CRC	59% (PR 4% + SD 55%)	Hand–foot syndrome 61% Fatigue 45% Hoarseness 24% Mucositis 24% Diarrhea 24% Anorexia 24% Hypertension 21%
Heisen, 2009 (N = 48)	Progressive, locally advanced or metastatic, previously untreated RCC	79% (PR 33% + SD 46%)	Hand–foot syndrome 61% Fatigue 51% Mucositis 45% Hypertension 41% Rash/desquamation 35% Alopecia 33% Diarrhea 31% Dysphonia 29% Anorexia 24%
Frost, 2008 (N = 33)	Progressive, locally advanced or metastatic solid tumors Represented histologies included CRC, melanoma and ovarian cancer	73% (PR 9% + SD 64%)	Hoarseness 54% Dermatological toxicity 50% Mucositis 35% Diarrhea 25% Fatigue 23% Hypertension 23%
Hedbom, 2007 (N = 22)	Progressive, locally advanced or metastatic solid tumors Represented histologies included CRC, RCC and pancreatic cancer	27% (PR 9% + SD 18%)	Hoarseness 32% Hypertension 23%
Kies, 2010 (N = 17)	Progressive, locally advanced or metastatic NSCLC	76% (PR 0% + SD 76%)	Hand–foot syndrome 35% Extremity pain 30% Hypothyroidism 26% Rash/desquamation 26%

CRC, colorectal cancer; RCC, renal cell cancer; NSCLC, non-small cell lung cancer; PR, partial response; SD, stable disease.

Forty-nine patients with untreated, metastatic or unresectable RCC were enrolled in a phase II trial of regorafenib. Patients had predominantly clear cell histology, low to intermediate risk according to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria, with an ECOG of 0-1, and received daily oral regorafenib at a dose of 160 mg for 21 days, followed by a 7-day rest period (19, 20). The primary study endpoint was response rate according to RECIST criteria; secondary objectives were safety, progression-free survival (PFS) and duration of response. Among the 45 evaluable patients, 13 (29%) achieved a confirmed PR according to RECIST criteria; an additional 4 patients had unconfirmed PR. Twenty-one patients experienced disease stabilization. Interestingly, 84% of the patients showed some degree of tumor shrinkage; among these, 15 had a reduction of > 40%. Seven patients experienced disease progression as their best response. Collectively, these data led to a disease control rate of 79%.

Plasma samples collected from 29 patients enrolled in the study at baseline and after 15 days of treatment were analyzed to gain insight into the activity of regorafenib (21). Some ligands to receptors targeted by regorafenib increased during treatment, such as placenta growth factor (PlGF), VEGF-A and -D and angiopoietin-2 (ANG-2), while some proangiogenic factors (c-Met, bFGF), as well as the soluble form of c-Kit, TIE-1 and VEGFR-2, decreased. Moreover, the levels of CK-18 M30 and cytochrome c, two proteins released following epithelial cell death, increased with response to treatment. Although the patient population was small, high baseline levels of soluble TIE-1, macrophage colony-stimulating factor (M-CSF), stem cell factor (SCF), tissue inhibitor of metalloproteinases 2 (TIMP-2), interleukin IL-16, Fas ligand and c-Met correlated with better clinical response to regorafenib. Adverse events were common, and included hand–foot syndrome and skin rash, fatigue, diarrhea, hypertension and mucositis. Renal failure due to

dehydration following vomiting and diarrhea was observed in four patients, leading to treatment discontinuation.

Strumberg et al. evaluated the activity of regorafenib in 38 patients with metastatic refractory CRC at doses of 60-220 mg/day for 21 days, followed by a 7-day rest period (22). Twenty-seven patients were evaluable for response. One patient showed a PR and 15 achieved SD, for a disease control rate of 59%. Analysis of plasma biomarkers demonstrated a decrease in soluble VEGFR-2 and an increase in VEGF during treatment (23). Moreover, Gd-DTPA uptake, measured by DCE-MRI, decreased during the study. However, these pharmacodynamic parameters did not correlate with PFS. The mutational analysis of *KRAS* was not predictive of response.

Recently, Shimizu and coworkers reported on a phase I dose-escalation study of regorafenib administered continuously in cycles of 21 days without planned rest periods (24). Thirty-eight patients with advanced solid tumors received 20-140 mg regorafenib orally once daily. Colorectal, thyroid, head and neck, and adenoid cystic carcinomas were among the most common histologies represented in patients enrolled in the study. Median treatment duration was 73 days. The clinical activity of regorafenib was 67%, with 2 PR and 22 SD over at least 6 weeks of treatment. The identified maximum tolerated dose for continuous daily administration of regorafenib was 100 mg/day orally. Common drug-related AEs were similar to the previous data, with skin toxicity as the most common dose-limiting toxicity observed.

The continuous schedule was selected by Kies and colleagues, who administered regorafenib at 100 (n = 22) or 120 (n = 1) mg/day on a 21-day cycle to 23 heavily pretreated metastatic NSCLC patients (25). Among the 17 evaluable patients, 13 had SD and 4 patients progressed. Hypothyroidism, a common AE seen with sunitinib and other kinase inhibitors, developed in 26% of the patients.

PERSPECTIVES AND ONGOING STUDIES

Regorafenib is undergoing extensive evaluation in phase II and III clinical trials as a single agent or in combination with standard chemotherapeutic agents in NSCLC (26), RCC (19, 20), CRC (27, 28) and HCC (29), based on the preliminary results of multiple phase I studies (Table III). These studies also include an extensive characterization of the pharmacokinetic and pharmacodynamic properties of the drug, along with the evaluation of potential biomarkers of response.

Kinase inhibitors and other targeted agents are generally effective in a subset of patients whose tumor is driven by a relevant kinase that is blocked by the tyrosine kinase inhibitor (5). In RCC, the efficacy of VEGFR kinase inhibitors is largely due to their antiangiogenic properties (30). GIST provided the first evidence for the efficacy of kinase inhibitors in solid tumors by virtue of the ability of imatinib to block oncogenic signals from activated c-Kit (4). GISTs are quite heterogeneous. Although the majority of GISTs, approximately 80%, carry an activating mutation in the coding sequence of *KIT,* 5% of tumors harbor a mutation in *PDGFRA* and 15% of tumors do not harbor an identifiable mutation in either *KIT* or *PDGFRA*. Since the efficacy of imatinib in GIST relies on its aforementioned ability to inhibit the mutated c-Kit kinase, the former group benefits the most from imatinib, while the latter groups have a much lower response rate (31). Unfortunately, resistance to kinase inhibitors eventually occurs, posing a major challenge to targeted agents. In GIST, the most common etiology of imatinib resistance is secondary mutations in *KIT* or *PDGFRA,* preventing the binding of imatinib to the receptor, and thereby allowing uncontrolled cell proliferation (32, 33).

Resistance in GIST is likely to be even more complex. It has been demonstrated that different metastatic lesions, within a given

Table III. *Actively recruiting studies.*

Disease	Patient characteristics	Study characteristics	Treatment schedule	Primary endpoints	Secondary endpoints
CRC	Stage IV CRC	Multicenter, open-label phase I study	Regorafenib 160 mg orally once daily, day 4 to day 10 + day 18 to day 24 + mFOLFOX6 or FOLFIRI	Safety, pharmacokinetics	Biomarkers, tumor response
CRC	Stage IV CRC	Randomized, double-blind, placebo-controlled phase III study	Arm I: regorafenib 160 mg orally once daily, 21 days on/7 days off + BSC Arm II: placebo + BSC	OS	PFS, ORR DCR, toxicity
NSCLC	Stage IIIB and IV nonsquamous NSCLC	Multicenter, open-label phase I study	Arm I: regorafenib 160 mg orally once daily, 14 days on/7 days off + cisplatin and pemetrexed Arm II: regorafenib 160 mg orally once daily continuously + cisplatin and pemetrexed	Safety, pharmacokinetics	Biomarkers, tumor response
GIST	Stage IV or unresectable GIST	Randomized, double-blind, placebo-controlled phase III study	Arm I: regorafenib 160 mg oral once daily, 21 days on/7 days off + BSC Arm II: placebo + BSC	PFS	OS, time to progression, DCR, response rate, DOR

CRC, colorectal cancer; NSCLC, non-small cell lung cancer; GIST, gastrointestinal stromal tumor; BSC, best supportive care; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; DCR, disease control rate; DOR, duration of response.

patient, do carry different secondary mutations. Moreover, little is known about the contribution of other kinases to the development of imatinib resistance in GISTs. In NSCLC, for example, *MET* amplification has been described as a mechanism of resistance to epidermal growth factor receptor (EGFR) inhibitors. Combination therapy with EGFR and c-Met inhibitors in this setting is under evaluation (34).

Sunitinib is the only FDA-approved drug for the treatment of GIST patients progressing on imatinib (35). Although sunitinib is a more potent inhibitor of c-Kit, its efficacy may be partly mediated by its antiangiogenic properties and its wider spectrum of kinase inhibition. In addition, sorafenib has demonstrated activity in patients with GISTs who failed standard treatments, with a reported disease control rate of 60-70% and a median PFS of 5 months (36), again suggesting that broader-spectrum kinase inhibition may be beneficial in GIST resistant to imatinib. Regorafenib has the broadest spectrum of inhibition among these kinase inhibitors, making this agent appealing for targeting multiple deregulated pathways. A phase II study exploring the activity of regorafenib in GISTs has recently completed accrual (37), and a phase III trial in GISTs is currently under way (38).

CONCLUSIONS

Regorafenib is a novel multikinase inhibitor, targeting VEGFR-2 and -3, TIE-2, PDGF-R-β, FGFR-1, c-Kit, Ret, c-RAF and MAP kinase p38. Its wide target profile may explain the broad antitumor activity in early phase I-II trials. However, whether a broad or narrow spectrum of inhibition is needed may vary among tumor types and stage of disease. It is noteworthy that, despite heavily pretreated patient populations, regorefenib has demonstrated notable activity in a variety of advanced solid tumors.

The evaluation of potential biomarkers of response remains a field of extensive investigation, which will remain critical to the development of new and effective, personalized anticancer treatments. A deeper understanding of the mechanisms of action of a drug will lead not only to better anticancer strategies, but, most importantly, avoid the dismissal of an active drug only because it has been tested in the wrong group of patients. Ongoing trials of regorafenib will provide a better understanding of which patient populations may optimally benefit from this novel agent.

SOURCE

Bayer AG (DE).

DISCLOSURES

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