Drugs of the Future 2013, 38(2): 81-89

CCC: 0377-8282/2013
DOI: 10.1358/dof.2013.38.2.1918242

DOVITINIB LACTATE

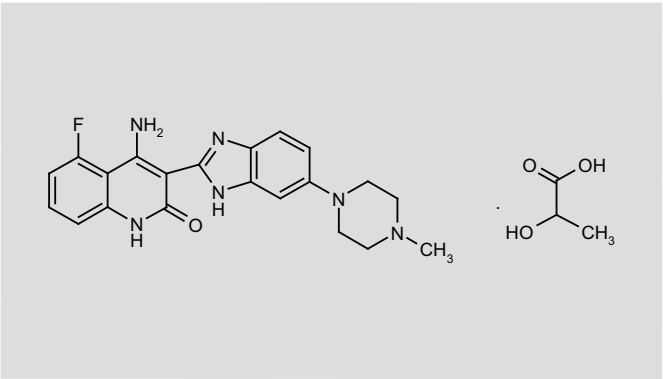
USAN

Multikinase Inhibitor
Antiangiogenic Agent
Oncolytic

Dovitinib (Rec INN)
TKI-258

4-Amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1*H*-benzimidazol-2-yl]quinolin-2(1*H*)-one lactate

InChI: 1S/C21H21FN6O.C3H6O3/c1-27-7-9-28(10-8-27)12-5-6-14-16(11-12)25-20(24-14)18-19(23)17-13(22)3-2-4-15(17)26-21(18)29;1-2(4)3(5)6/h2-6,11H,7-10H2,1H3,(H,24,25)(H3,23,26,29);2,4H,1H3,(H,5,6)



$C_{21}H_{21}FN_6O.C_3H_6O_3$
Mol wt: 482.5074
CAS: 915769-50-5
CAS: 405169-16-6 (free base)
EN: 343725

SUMMARY

Angiogenesis is a key and rate-limiting process for malignant tumor growth. Antiangiogenic agents targeting the vascular endothelial growth factor (VEGF)/vascular endothelial growth factor receptor 2 (VEGFR-2) axis have demonstrated activity in different cancers; however, resistance develops due to the upregulation of other proangiogenic axes (fibroblast growth factor receptor [FGFR]/platelet-derived growth factor receptor [PDGFR] families). Dovitinib lactate is a small-molecule multikinase inhibitor that targets not only several proangiogenic axes, but some oncogenic kinases driving malignancies such as gastrointestinal stromal tumors (GIST), acute myeloid leukemia (AML) or bladder carcinoma. This dual effect was evidenced by potent growth inhibition of both highly angiogenesis-dependent tumors and oncogenic kinase-driven tumors in preclinical mouse models. Dovitinib lactate is administered orally, it has a t_{max} of approximately 4 hours, a high volume of distribution and a long terminal half-life, and administration on a 5-days-on/2-days-off schedule resulted in manageable toxicity (mainly gastrointestinal and transaminitis) and no accumulation. Promising preliminary activity was observed in liver and kidney cancer, as well as myeloma and AML.

Key words: Antiangiogenic agent – Tumors – Multikinase inhibitor – Dovitinib lactate – Dovitinib – TKI-258

M. Quintela-Fandino[1,2] and R. Colomer[1,3]. [1]CNIO – Spanish National Cancer Research Center, Madrid, Spain; [2]MD Anderson International, Madrid, Spain; [3]Hospital La Princesa, Madrid, Spain. E-mail: mquintela@cnio.es.
*Synthesis prepared by J. Bolòs, R. Castañer. Thomson Reuters, Provença 398, 08025 Barcelona, Spain.

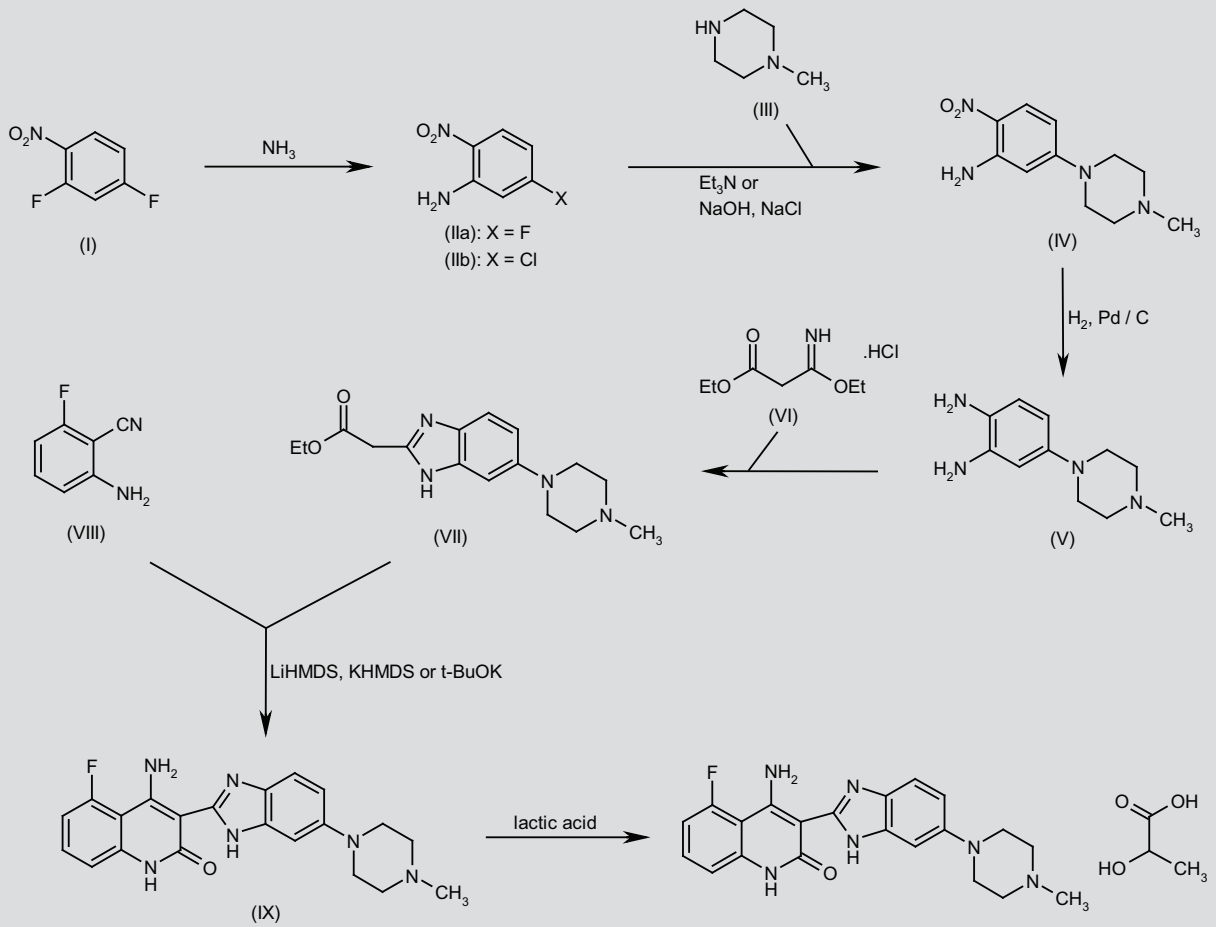
SYNTHESIS*

Reaction of 2,4-difluoronitrobenzene (I) with liquid ammonia gives 5-fluoro-2-nitroaniline (IIa) (1-4), which by subsequent displacement of the remaining fluoride group with *N*-methylpiperazine (III) in the presence of Et_3N in NMP at 100 °C provides the piperazinyl aniline (IV) (1-5). Alternatively, nitroaniline (IV) can be prepared by condensation of 5-chloro-2-nitroaniline (IIb) with *N*-methylpiperazine (III) in hot EtOH (4, 6, 7), ethylene glycol or aqueous NaCl, optionally in the presence of NaOH (6). Catalytic hydrogenation of nitroaniline (IV) over Pd/C in EtOH at 40-45 °C yields the phenyldiamine (V) (1-7), which by condensation with ethyl 3-ethoxy-3-iminopropionate hydrochloride (VI) at reflux produces benzimidazole (VII) (1, 3, 4-7). Cyclocondensation of ethyl ester (VII) with 2-amino-6-fluorobenzonitrile (VIII) (1, 3, 4-7) by means of LiHMDS (1, 3, 5), KHMDS or *t*-BuOK in THF or toluene (4, 6, 7) furnishes dovitinib (IX) (1, 3, 4-7), which is finally treated with racemic lactic acid in EtOH/H_2O (4, 6, 7). Scheme 1.

BACKGROUND

Angiogenesis is a process consisting of the development of novel blood vessels from existing ones, mainly through replication, differentiation and mobilization of endothelial cells, pericytes and fibroblasts. It is a key tumor progression factor and a rate-limiting step for tumor growth (8). Several tumor features, such as the replication rate, metabolic needs and cell/stroma ratio, condition the high or

Scheme 1. Synthesis of Dovitinib Lactate



low angiogenic needs (9). However, despite these different needs, tumor growth is not possible beyond (approximately) 0.1 mm in the absence of angiogenesis. Thus, Judah Folkmann hypothesized in the 70s that controlling tumor angiogenesis would be sufficient to control oncological diseases in a subclinical state, as no tumor mass would be able to grow macroscopically (10, 11).

The first discovered and characterized proangiogenic signaling axis was vascular endothelial growth factor (VEGF)–vascular endothelial growth factor receptor 2 (VEGFR-2) (10). Clinical and preclinical studies soon demonstrated the existence of many redundant systems (12), in part evidenced by the acquired resistance occurring in virtually all patients exposed to anti-VEGF agents in the metastatic setting. In addition to acquired resistance, some tumors show primary refractoriness to VEGF-targeting agents as well (13). Currently, several receptor families with different isoforms and cross-talk and cross-activation with their different ligands have been described and implicated in this process, including VEGFR, platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), TGF-beta receptor (TGFR) and tyrosine-protein kinase receptor Tie families (8, 12, 13). Thus, second-generation agents blocking several of the novel elucidated signaling systems were developed, although the relatively high K_m and thus frequent off-target effects made by these agents, while effective, are difficult to tolerate (14-17). A novel, third generation of this class has entered clinical development during the last 4 years, which could be named "antistromal therapies", as they target many of the signaling axes of the host's aberrantly functioning, tumor cell-induced reprogrammed stromal compartments: fibroblasts (FGFR family), immune cells (SCF, c-Kit), endothelial cells (VEGFR family), pericytes (PDGFR family), or others. These third-generation antistromal agents are highly effective and better tolerated than their predecessors (18-21). In addition, depending on their inhibitory profile, they have direct antitumor properties, targeting oncogenic addiction-driving genetic hits, such as *FGFR* amplification (relevant in some cases of breast cancer) (22-25), *KIT* and/or *PDGFR* mutations (GIST) (26), *RET* mutations (thy-

roid cancer) (27) or *FLT3* mutations (acute myeloid leukemia [AML]) (28, 29). This combination of antistromal effects and cytotoxic properties in the tumor cases originated by the mentioned driver events, together with the manageable toxicity, make this class of agents extremely interesting for cancer therapy. Several cancer types are highly dependent on angiogenesis, such as kidney (30-33), liver (34-37), thyroid (38-40) or neuroendocrine cancers (41, 42); preclinical and clinical evidence sustains the activity of antistromal agents administered as monotherapy against them (30-42). In addition, studies in combination with chemotherapy in some malignancies suggest that the efficacy of the combination could be synergistic (43-47). Lastly, these agents cause prolonged and durable complete remissions in the rare cancer types driven by the oncogenic addictive events mentioned above (48-50).

Dovitinib lactate (TKI-258) is an inhibitor of type III, IV and V receptor tyrosine kinases (RTKs) that mediate both endothelial and tumor cell proliferation and survival (51, 52). Dovitinib lactate is a potent inhibitor of the PDGFR, VEGFR and FGFR families, as well as mutant *RET*, *KIT* and *FLT3*. The current monograph focuses on its preclinical pharmacology, pharmacokinetics and pharmacodynamics, as well as activity data; finally, we will also discuss current areas of clinical development.

PRECLINICAL PHARMACOLOGY

Dovitinib lactate demonstrated activity in a number of in vitro and in vivo models. It potently inhibits the activity of multiple RTKs, including PDGFR-β (in vitro IC_{50} = 30 nM), macrophage colony-stimulating factor 1 receptor (CSF-1R; 15 nM), proto-oncogene c-Kit (2 nM), FLT-3 (1 nM), VEGFR-1, -2 and -3 (8-15 nM), tyrosine kinase receptor A (Trk-A; 9 nM), proto-oncogene c-Ret (7 nM) and FGFR-1/2 (20-40 nM) and FGFR-3 (5 nM) (46). In vitro cell proliferation EC_{50} values in cells expressing either target ranged from 13 nM (M4C cells with *FLT3* tandem duplication) to 211 (human osteosarcoma MG-63 cells with PDGFA/PDGFB expression). Breast cancer SUM52 cells with *FGFR2* amplification or bladder carcinoma RT-112 cells with *FGFR3* overexpression showed an EC_{50} of approximately 150 nM. Interestingly, non-cancer cell lines such as HMEC (normal breast) and PrC (normal prostate) showed an almost 1,000-fold higher EC_{50}, suggesting a good therapeutic index (53). The activity of dovitinib lactate therefore has a dual antitumor effect, as some of the targeted kinases are involved in direct protumorigenic kinases causing oncogenic addiction (i.e., FGFR or RET), and others in stromal tumor cross-talk. Regarding this second matter, dovitinib lactate extends its activity over classic antiangiogenic agents, targeting not only the VEGFR axis (thus modulating the survival of endothelial cells), but also the FGFR and PDGFR systems as well (playing a role in tumor fibroblast reprogramming and pericyte physiology, respectively).

ERK phosphorylation in VEGFR-expressing human umbilical vein endothelial cells (HUVECs) in response to VEGF stimulation is completely abrogated at 100 nM. Dovitinib inhibited angiogenesis in an FGF-driven murine model of neovascularization, with a minimum effective dose (MED) of 3 mg/kg/day (9 mg/m^2) (54). Studies in the RIP-Tag-based experimental mouse tumor model have shown that tumor angiogenesis can switch from VEGFR dependence to FGFR dependence under anti-VEGF therapy (41). This mechanism could explain treatment failure with agents targeting single angiogenic targets. As dovitinib lactate combines activity against both targets, and renal cell carcinoma is the tumor type most dependent on angiogenesis due to the VHL mutations, two murine models of renal cancer consisting of RENCA and 786-O xenografts (wild-type and mutant Von Hippel-Lindau [VHL] syndrome, respectively) were tested for efficacy in VEGF-targeting alone, sorafenib, sunitinib (antiangiogenic agents with activity against VEGFR and PDGFR) and dovitinib lactate. Dovitinib lactate produced at least a 30% greater antitumor efficacy than either of the agents (53, 55, 56). Dovitinib lactate treatment in additional oncology models of diverse tumor origin but not target-driven, including colon, myeloma, prostate, ovarian, lung, renal cell carcinoma and hepatocellular carcinoma, also resulted in tumor regression, stabilization or growth inhibition. According to the angiogenesis dependency, the highest benefit in these models was observed in hepatocellular carcinoma (57-59).

According to the predicted double-edged activity, antistromal and antioncogenic addiction targets, dovitinib lactate showed considerable antitumor activity as well in target-driven models. Trudel and colleagues demonstrated in a multiple myeloma xenograft model characterized by a 4,14 chromosomal translocation that results in ectopic increased expression of FGFR3, a sevenfold delay in tumor growth compared with vehicle when treating the animals with dovitinib lactate. In addition, dovitinib lactate induced apoptosis in primary cells established from patients with this translocation; interestingly, the effect was preserved when trying to induce therapeutic resistance with insulin-like growth factor I (IGF-I) or interleukin-6 (IL-6) (51).

In another target-driven model, AML, dovitinib lactate demonstrated activity as well. Two xenograft models, RS4;11 and MV-4-11, characterized by wild-type and mutant *FLT3*, respectively, were tested; the activity was 24-fold higher in the mutant model, suggesting the high potential activity of oncogenic addiction event-driven cancers (60). Efficacy against a myeloproliferative syndrome driven by the 8p11 translocation (atypical stem cell myeloproliferative disorder associated with a rearrangement that results in disruption and constitutive activation of *FGFR1* by a fusion gene) (61) and against *FGFR3*-driven Waldenström macroglobulinemia (62), was demonstrated as well.

The target-driven efficacy is not limited to clonal malignancies such as hematological tumors. Similar results were obtained in *FGFR3*-mutant driven and *FGFR1*-overexpressing urothelial cancer (23). Table I summarizes the most representative preclinical studies performed in murine models.

In agreement with what would be expected, although tumor regression, or at least growth delay, was observed virtually with any tumor model tested, the AUC required for non-target-driven models or less angiogenesis-dependent models than liver or kidney cancer was approximately threefold higher (63).

PHARMACOKINETICS AND METABOLISM

Dovitinib lactate has a variable bioavailability in preclinical models, ranging from 20% in dogs to more than 70% in rats, mice and monkeys. Apparently, this variability is due to pH changes from one species to another, as dovitinib lactate is less soluble in higher pH solutions. Once absorbed, dovitinib lactate is highly bound to plas-

Table I. *Summary of preclinical studies conducted in mouse models.*

	Studies targeting angiogenesis			
Model	Tumor type	Target	Treatment	Result
KMS-11-Luc (xenograft)	MM	VEGFR-independent angiogenesis	Dovitinib alone	Decrease in tumor growth and angiogenesis, improvement in mouse survival
RENCA and 786-O (xenograft)	Wild-type and mutant VHL kidney cancer, respectively	Angiogenesis	Dovitinib compared to sorafenib or sunitinib	At least 30% improvement in efficacy (tumor growth) for dovitinib
HuH-7 and PLC-5 (xenograft)	Hepatocellular carcinoma resistant to sorafenib	Angiogenesis	Dovitinib compared to sorafenib	Decrease in tumor growth compared to no effect with sorafenib
	Studies targeting oncogenic addiction drivers			
Model	Tumor type	Target	Treatment	Result
KMS-11-Luc (xenograft)	Mutant FGFR-3-driven MM	Mutant FGFR-3	Dovitinib alone	Improvement in overall survival, decrease in tumor growth
RS411 and MV-4-11 (xenograft)	Wild-type and mutant FLT3-driven AML	Mutant FLT-3	Dovitinib alone	24-Fold higher activity in the mutant model
Various (xenograft)	Mutant and amplified FGFR-1, -2 and -3-driven bladder cancer vs. wild-type bladder cancer	FGFR-1, -2 and -3	Dovitinib or PD-173074 (activity against activated FGFRs) vs. SU-5402	In the mutant or amplified models the activity of dovitinib or PD-173074 was three orders of magnitude higher

MM, multiple myeloma; AML, acute myeloid leukemia.

ma proteins. The t_{max} varies as well from 2 to 8 hours depending on the animal model, but the t_{max} is not subjected to variability, interestingly, due to single or multiple doses or dose levels. The distribution in the body is > 90% in tissue versus blood, revealed by the very large volumes of distribution (90 L/kg) observed in large animals; in tumor xenograft studies, the tissue/plasma concentration was above 200-fold as well. The terminal half-life of the agent was consistently observed in approximately 3 hours in all tested species; however, radioactivity studies with labeled compound (showing the time to elimination of both dovitinib lactate and all the metabolites) was much longer, ranging from 6 hours in mice to 40 hours in monkeys. Food did not appear to modulate pharmacokinetic data.

Several pharmacokinetic parameters (C_{max}, AUC) showed a linear correlation with dovitinib lactate dose, both following oral and intravenous administration. However, these parameters suggested a metabolic induction effect, as the plasma exposure results following repeated doses (up to 28 days) were lower than those obtained from single-dose experiments. This plasma exposure decrease was observed across the different species tested, i.e., dogs, monkeys and rats (53).

Following incubation of dovitinib lactate with liver microsomes from the various species tested, two major metabolites were identified: *N*-desmethyl (M8) and *N*-oxide (M9). M8 has a potency similar to dovitinib lactate in cell proliferation assays; however, M9 is approximately 5- to 10-fold less active (53).

Regarding enzymatic induction/inhibition studies, dovitinib lactate was evaluated in primary cultures of human, monkey, rat and dog hepatocytes. No induction of cytochrome P450 2B or 3A was observed, although the induction of 1A and 2C9/19 was observed. In pooled human hepatic microsomes, dovitinib lactate demonstrated virtually no clinically relevant inhibitory potential for five major human hepatic cDNA-derived CYP450 isozymes (CYP 1A2, 2C9, 2C19, 2D6 and 3A4), as evidenced by an IC_{50} of > 25 mM. None of its metabolites were able to inhibit these isozymes either. Thus, it is unlikely that dovitinib lactate would lead to inhibitory drug–drug interactions when coadministered with drugs metabolized by the major CYP450s (53).

In humans, the ADME (absorption, distribution, metabolism and excretion) study provided thorough pharmacokinetic data for this agent. No food effect was observed in humans and the bioavailability of a single dose was about 75%. More than 95% of the agent bound to albumin, and a high apparent volume of distribution was observed (30 L/kg). The elimination occurred mainly via metabolism. The biotransformations observed were mainly oxidative, yielding the known M8 and M9 metabolites among others. Direct glucuronidation was observed as well. Less than 7% of unchanged dovitinib lactate was recovered in urine; thus, the contribution of renal excretion to the elimination of dovitinib lactate was judged to be minimal. Approximately 5-20% of the unchanged compound was recovered in feces. Single-dose administration evidenced a terminal half-life of approximately 28 hours, which decreased to approximately 13 hours at the steady state of continuous administration. According to the biotransformation reactions, most of the radioactivity was recovered from the feces (up to 70%), consistent with the fecal elimination of most of the dovitinib lactate metabolites. The contribution of urinary excretion was low, with 13-21% of the radioactivity recovered from urine. Food effect studies recommend taking dovitinib lactate without food or with a low-fat meal (53).

Only two clinical trials studying dovitinib lactate's pharmacokinetics have been finished and fully published (64, 65). C_{max} was observed at approximately 4-8 hours after dosing, and the concentration of dovitinib lactate declined monoexponentially thereafter. Within the tested dose levels ranging from 25 to 600 mg/day, linear absorption of dovitinib lactate was observed. Dovitinib lactate was extensively distributed into tissues.

Time-dependent pharmacokinetics for dovitinib lactate were observed across all tested dose levels. Following daily administration at doses below 400 mg, auto-induction of CYP 1A1/A2 resulted in lower plasma exposure of dovitinib lactate on day 7 (steady state) than that observed on day 1 (65, 66). However, after increasing the daily dose to 400-600 mg, dovitinib lactate plasma concentration on day 7 was found to be similar to or greater than that on day 1, suggesting a more pronounced accumulation of dovitinib lactate at higher doses. In addition, an over-proportional increase in dovitinib lactate plasma exposure was observed with doses from 400 to 600 mg/day. The time-dependent pharmacokinetics and the nonlinear pharmacokinetics resulted in a dose-dependent time to reach steady state, as well as dose-dependent accumulation at steady state. To prevent the prolonged and over-proportional accumulation in dovitinib lactate exposure with dose escalation, an intermittent dosing schedule of 5 days on/2 days off was proposed. At tested dose levels of 500 and 600 mg, no accumulation was observed on day 15 (steady state). The maximum tolerated dose for the 5-days-on/2-days-off dosing schedule was 500 mg, which is the dose recommended for clinical studies (64). At this dose level, the median AUC and the C_{max} were, on day 1 (n = 6 patients) and day 15 (n = 6 patients), 322.8 ng*h/mL and 199 ng/mL, and 3179 ng*h/mL and 227.5 ng/mL, respectively. These differences were non-statistically significant, consistent with the absence of accumulation observed with the 5-days-on/2-days-off schedule.

SAFETY

Several preclinical studies on toxicity have been performed with short- and long-term daily doses (4 weeks and 28 weeks, respectively, followed by a recovery period) of dovitinib lactate in Sprague-Dawley rats, Beagle dogs and cynomolgus monkeys (only 28-day treatment). In each species, different dose levels were tried (10-100 mg/kg in rats, 1-10 mg/kg in dogs and 0-80 mg/kg in monkeys). Rats on the 100 mg/kg dose level had to be euthanized due to severe weight loss. Several target organs for toxicity were recognized in autopsies: necrosis of the adrenal cortex, lymphoid depletion of the thymus, lymph nodes and spleen, multiple glandular atrophy and bone marrow depression. Bone marrow changes at 10 and 30 mg/kg were mild. At 100 mg/kg, single cell liver necrosis and hepatocellular vacuolation was observed, together with increased gamma-glutamyltransferase and decreased albumin, coupled with increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin. Although moderate elevations in liver enzymes were seen at 10 and 30 mg/kg, no histopathological changes were observed. Long-term administration of 30 mg/kg was non-tolerable for male rats due to weight loss, and treatment had to be suspended for 1 week after 8 consecutive weeks of treatment, restarting at 20 mg/kg. Females tolerated long-term treatment. Bone marrow depression, increases in transaminases and decrease in albumin were observed but reversible after the recovery period. However, vacuolization, hypertrophy and pigment accumulation were poorly reversible. Dental anomalies, probably due to a VEGF/FGF homeostasis alteration, were observed in the long-term groups as well (53).

In dogs, emesis was the limiting toxicity, although with no microscopic correlates in the gastrointestinal tract, at 10 mg/kg. Weight loss was observed at the same dose level, but no bone marrow depression or cardiac toxicity. Long-term administration did not cause changes in ophthalmological exams, ECGs or organ weights, although weight loss with liver lesions was observed in some animals. Emesis and diarrhea occurred at the 3 mg/kg dose level in females and at 10 mg/kg in males; animals with these symptoms suffered from weight loss as well. Moderate hematological and hepatic blood parameters were observed at 3 and 10 mg/kg. Hepatic parameter alterations were coupled with microscopic liver changes, such as fibrosis, infiltration by mature neutrophils and hyperplasia of bile ducts. These changes were not reversible after a 4-week recovery period (53).

Finally, in monkeys, 30 and 80 mg/kg were not tolerable, animals having to be sacrificed after 19 days of continuous treatment. Emesis, low food intake, watery stools and severe body weight loss were observed at these levels, together with bone marrow depression signs and liver parameter alterations. Other changes at this dose level included myocardial degeneration associated with inflammation, kidney tubular degeneration, liver hepatocyte hypertrophy, thymus atrophy and intestinal mucosal damage (53).

The physiology of normal blood vessel development, both during pre- and postnatal growth, requires a tight balance between pro- and antiangiogenic factors. Knockout murine models of either pro- or antiangiogenic signaling nodes are usually lethal during early embryonic stages. Thus, it is not surprising that dovitinib lactate, due to its high selectivity over VEGFR, PDGFR and FGFR receptor families, is linked to defective embryo development; actually, teratogenicity was confirmed in a preclinical study (46), and thus dovitinib lactate should not be administered to pregnant women and the teratogenic potential should be advised to fertile women who are not using effective contraceptive methods.

Dovitinib lactate has demonstrated genotoxic potential and is therefore inappropriate to administer to healthy volunteers. Thus, human toxicity data are available only on the basis of clinical trials in cancer patients. To date, only two phase I clinical trials have been fully reported. The first clinical trial used a continuous dosing schedule (65). Among 35 patients enrolled, most of the reported adverse events were grade 1 or 2 according to the NCI CTCAE v4.0. The most commonly reported events were fatigue, anemia, nausea, vomiting, diarrhea, headache, anorexia, hypertension and alkaline phosphatase elevation. There were two episodes of grade 2 reduced left ventricular ejection fraction and one asymptomatic pulmonary embolism. Hypertension and ventricular ejection toxicity required treatment in two and one patient, respectively. Dose-limiting toxicities were asymptomatic grade 3 alkaline phosphatase elevation (1 patient), grade 3 hypertension (1 patient) and grade 3 anorexia (1 patient) (64). The toxicity profile is congruent with other antivascular and multikinase inhibitor agents.

CLINICAL STUDIES

Dovitinib lactate is being studied mainly in breast cancer, endometrial cancer, hepatocellular carcinoma, urothelial tumors and renal cell carcinoma, among other solid tumors. In addition, it is under evaluation in several hematological malignancies, such as multiple myeloma and AML.

Currently, only two trials have been finished and published. Both these trials were phase I studies. Due to the advanced stages and the heavily pretreated nature of the patients included in these trials, it is challenging to extract formal conclusions about its activity. A total of 82 patients have been enrolled in phase I trials (64, 65), suggesting activity mainly in melanoma. However, due to the inherent selection bias of phase I trials, these results should be taken with caution.

There are currently three types of ongoing clinical trials: trials studying the efficacy of dovitinib lactate (15; 3 of them in combination with other agents), phase I trials studying the safety and preliminary efficacy of dovitinib in combination with other agents (5 trials; 1 of each exploring the combination with erlotinib, paclitaxel, gem-citabine plus carboplatin, dexamethasone plus bortezomib [only in multiple myeloma patients] and gemcitabine plus capecitabine), and 3 trials pursuing other objectives (pharmacokinetic knowledge refinement, biomarker definition or food effect). Only two of these trials (one efficacy study in endometrial carcinoma and the phase I trial exploring the combination with paclitaxel) select the patients by driving oncogenic mutations targetable by dovitinib lactate. The first of them includes patients stratifying them by *FGFR2* mutational status, whereas the second screens for > 30 mutations in the FGFR-1, -2 and -3 and Ret receptors, and/or amplifications in either of the FGFRs as inclusion criterion. The summary of the ongoing clinical trials assessing efficacy is included in Table II.

CONCLUSIONS

Overall, dovitinib lactate appears to be a very well tolerated, third-generation antistromal agent with a broad kinase inhibitor profile, demonstrating in preclinical models very promising activity not only at the stromal level, but also at driving the oncogenic kinase level as well. Combined blockade of many kinases may or may not be a better strategy than just a few; indeed, each pro- or antiangiogenic factor at the tumor microenvironment plays a role in the final vascular normalization status of the tumor, and thus tumor oxygenation and chemotherapy delivery. Currently, it is not possible to predict the effect of the manipulation of one single signaling system on the normalization status at the individual level, as either an excess or a deficit in one single factor or system can lead to vessel abnormalities, and ultimately, tumor progression. Alternatively, blockade of an excessive number of kinases may lead to unacceptable side effects. For example, a clinical trial, NCT01441414, that combined an angiopoietin (Tie-2 ligand) inhibitor and axitinib, a multikinase inhibitor antiangiogenic agent, had to be terminated due to vascular toxic events (67). The potential advantage of dovitinib lactate is that

Table II. *Summary of ongoing efficacy trials (registered at www.clinicaltrials.gov). All trials are exploring the efficacy in advanced disease stages.*

NCT registration	Cancer type	Trial phase	Efficacy endpoint	Target n	Expected accrual completion
NCT01379534	Endometrial	II	18-week PFS rate, stratified by FGFR-2 genotype	80	Jan-15
NCT01232296	Liver	II (randomized)	OS (sorafenib vs. dovitinib)	165	Jul-13
NCT01576380	Scirrhous gastric	II	DCR	45	Nov-14
NCT01524692	Adenoid cystic	II	RR	10	Jan-14
NCT01635907	NET	II	N/A	22	Jun-15
NCT01266070	VHL	I-II	RR*	25	Oct-15
NCT01262027	Breast	II	RR	33	Jan-16
NCT01528345	Breast (HHRR+)	II	PFS**	150	Oct-14
NCT01676714	Colon and NSCLC	II	RR and biomarkers	35	Oct-14
NCT01484041	Breast (HHRR+)	I/II	CBR***	36	Dec-15
NCT01514526	Adrenocortical	II	ORR	17	Jul-13
NCT01678105	Adenoid cystic	II	PFS	20	Sep-13
NCT01417143	Adenoid cystic	II	OS	33	Sep-13
NCT01223027	Kidney	III	PFS sorafenib vs. dovitinib	550	May-13
NCT01478373	GIST (resistant to imatinib)	II	DCR	36	Dec-13

NET, neuroendocrine tumor; VHL, Von Hippel-Lindau syndrome; HHRR+, hormonal receptor-positive; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; DCR, disease control rate; RR, tumor response rate; CBR, clinical benefit rate, defined as complete response plus partial response plus disease stabilization rate; N/A, not available. *This trial is assessing safety as well. **Fulvestrant is administered in combination with dovitinib. ***Dovitinib in combination with an aromatase inhibitor. The phase I part will assess the safety of the combination.

on top of blocking a set of pathological angiogenesis driver signaling systems that has already proven to be beneficial, instead of modulating other angiogenic kinases, it targets oncogenes such as *FLT3* or *KIT*, thus extending its potential applications. Formal efficacy studies in pathologies such as kidney and liver carcinoma, where dovitinib lactate is being compared prospectively against reference therapies, and data from the genetically selected patient trials are eagerly awaited.

DRUG INTERACTIONS

To date, there are no formal drug–drug interaction studies reported. As mentioned above, the in vitro studies demonstrated a low inhibitory capacity of CYP450s; thus, it is not expected that dovitinib lactate would cause inhibitory drug–drug interactions when administered together with drugs degraded by the CYP450s. Finally, dovitinib lactate demonstrated induction capacity of CYP 1A2, 2C9 and 2C19; thus, coadministration of dovitinib lactate with substrates of those CYPs could reduce the exposure of those drugs.

SOURCE

Novartis AG (CH).

ACKNOWLEDGMENTS/DISCLOSURES

Miguel Quintela-Fandino is a recipient of the following grants: FIS PI10/288 ("Fondo de Investigación Sanitaria – Ministerio de Sanidad" – Health Research Funds, Ministry of Health); AECC 2010 "Becas de Retorno" (Spanish League Against Cancer); and a donation from AVON España. Miguel Quintela-Fandino has received research funding from Novartis Spain, and is the principal investigator of an investigator-sponsored clinical trial with dovitinib lactate (NCT01548924).

REFERENCES

1. Machajewski, T., Shafer, C., McCrea, B. et al. (Novartis Vaccines and Diagnostics, Inc.). *Quinolone derivatives*. EP 1317442, EP 1650203, EP 1849782, JP 2004509112, US 2002107392, US 6605617, WO 2002022598.
2. Harrison, S.D., Shafer, C.M., Pecchi, S. et al. (Novartis Vaccines and Diagnostics, Inc.). *Benzimidazole quinolines and uses thereof*. EP 1539754, JP 2006503919, JP 2011162563, US 200409235, US 2013018058, WO 2004018419.
3. Renhowe, P.A., Pecchi, S., Machajewski, T.D. (Novartis Vaccines and Diagnostics, Inc.). *Quinolone derivatives*. JP 2005527587, US 2003028018, WO 2003087095.
4. Cai, S., Chou, J., Harwood, E., Machajewski, T.D., Ryckman, D., Shang, X., Zhu, S. (Novartis Vaccines and Diagnostics, Inc.). *Pharmaceutically acceptable salts of quinolinone compounds having improved pharmaceutical properties*. CN 102225926, EP 1699421, JP 2007522098, JP 2011042687, WO 2005046589.
5. Renhowe, P.A., Pecchi, S., Shafer, C.M. et al. *Design, structure-activity relationships and in vivo characterization of 4-amino-3-benzimidazol-2-ylhydroquinolin-2-ones: A novel class of receptor tyrosine kinase inhibitors.* J Med Chem 2009, 52(2): 278-92.
6. Calvin, G., Harwood, E., Ryckman, D., Zhu, S. (Novartis AG). *Methods for synthesizing heterocyclic compounds*. EP 1888556, EP 2465857, JP 2008540675, US 2011046376, US 8222413, WO 2006125130.
7. Okhamafe, A., Chou, J., Gullapalli, R., Harwood, E., Ryckman, D., Zhu, S., Shang, X. (Novartis Corp.). *Crystalline and other forms of 4-amino-5-fluoro-3-[6-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-quinolin-2-one lactic acid salts*. CN 102070614, EP 1904480, EP 2266974, EP 2270000, JP 200854289, US 2011178097, US 2012208825, WO 2006127926.
8. Chung, A.S., Lee, J., Ferrara, N. *Targeting the tumour vasculature: Insights from physiological angiogenesis.* Nat Rev Cancer 2010, 10(7): 505-14.
9. Hlatky, L., Hahnfeldt, P., Folkman, J. *Clinical application of antiangiogenic therapy: Microvessel density, what it does and doesn't tell us.* J Natl Cancer Inst 2002, 94(12): 883-93.
10. Folkman, J., Merler, E., Abernathy, C., Williams, G. *Isolation of a tumor factor responsible for angiogenesis.* J Exp Med 1971, 133(2): 275-88.
11. Folkman, J. *Tumor angiogenesis: Therapeutic implications.* N Engl J Med 1971, 285(21): 1182-6.
12. Sennino, B., McDonald, D.M. *Controlling escape from angiogenesis inhibitors.* Nat Rev Cancer 2012, 12(10): 699-709.
13. Bergers, G., Hanahan, D. *Modes of resistance to anti-angiogenic therapy.* Nat Rev Cancer 2008, 8(8): 592-603.
14. Llovet, J.M., Ricci, S., Mazzaferro, V. et al. *Sorafenib in advanced hepatocellular carcinoma.* N Engl J Med 2008, 359(4): 378-90.
15. Escudier, B., Eisen, T., Stadler, W.M. et al. *Sorafenib in advanced clear-cell renal-cell carcinoma.* N Engl J Med 2007, 356(2): 125-34.
16. Raymond, E., Dahan, L., Raoul, J.L. et al. *Sunitinib malate for the treatment of pancreatic neuroendocrine tumors.* N Engl J Med 2011, 364(6): 501-13.
17. Motzer, R.J., Hutson, T.E., Tomczak, P. et al. *Sunitinib versus interferon alfa in metastatic renal-cell carcinoma.* N Engl J Med 2007, 356(2): 115-24.
18. Rini, B.I., Escudier, B., Tomczak, P. et al. *Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): A randomised phase 3 trial.* Lancet 2011, 378(9807): 1931-9.
19. van der Graaf, W.T., Blay, J.Y., Chawla, S.P. et al. *Pazopanib for metastatic soft-tissue sarcoma (PALETTE): A randomised, double-blind, placebo-controlled phase 3 trial.* Lancet 2012, 379(9829): 1879-86.
20. Sternberg, C.N., Davis, I.D., Mardiak, J. et al. *Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial.* J Clin Oncol 2010, 28(6): 1061-8.
21. Ledermann, J.A., Hackshaw, A., Kaye, S. et al. *Randomized phase II placebo-controlled trial of maintenance therapy using the oral triple angiokinase inhibitor BIBF 1120 after chemotherapy for relapsed ovarian cancer.* J Clin Oncol 2011, 29(28): 3798-804.
22. Shiang, C.Y., Qi, Y., Wang, B. et al. *Amplification of fibroblast growth factor receptor-1 in breast cancer and the effects of brivanib alaninate.* Breast Cancer Res Treat 2010, 123(3): 747-55.
23. Lamont, F.R., Tomlinson, D.C., Cooper, P.A., Shnyder, S.D., Chester, J.D., Knowles, M.A. *Small molecule FGF receptor inhibitors block FGFR-dependent urothelial carcinoma growth in vitro and in vivo.* Br J Cancer 2011, 104(1): 75-82.
24. Gozgit, J.M., Wong, M.J., Moran, L. et al. *Ponatinib (AP24534), a multitargeted pan-FGFR inhibitor with activity in multiple FGFR-amplified or mutated cancer models.* Mol Cancer Ther 2012, 11(3): 690-9.
25. Dodurga, Y., Tataroglu, C., Kesen, Z., Satiroglu-Tufan, N.L. *Incidence of fibroblast growth factor receptor 3 gene (FGFR3) A248C, S249C, G372C, and T375C mutations in bladder cancer.* Genet Mol Res 2011, 10(1): 86-95.
26. Corless, C.L., Barnett, C.M., Heinrich, M.C. *Gastrointestinal stromal tumours: Origin and molecular oncology.* Nat Rev Cancer 2011, 11(12): 865-78.

27. Nikiforov, Y.E., Nikiforova, M.N. *Molecular genetics and diagnosis of thyroid cancer.* Nat Rev Endocrinol 2011, 7(10): 569-80.
28. Stirewalt, D.L., Radich, J.P. *The role of FLT3 in haematopoietic malignancies.* Nat Rev Cancer 2003, 3(9): 650-65.
29. Langdon, W.Y. *FLT3 signaling and the development of inhibitors that target FLT3 kinase activity.* Crit Rev Oncog 2012, 17(2): 199-209.
30. Gnarra, J.R., Tory, K., Weng, Y. et al. *Mutations of the VHL tumour suppressor gene in renal carcinoma.* Nat Genet 1994, 7(1): 85-90.
31. Iliopoulos, O., Levy, A.P., Jiang, C., Kaelin, W.G., Jr., Goldberg, M.A. *Negative regulation of hypoxia-inducible genes by the von Hippel-Lindau protein.* Proc Natl Acad Sci U S A 1996, 93(20): 10595-9.
32. Maxwell, P.H., Wiesener, M.S., Chang, G.W. et al. *The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis.* Nature 1999, 399(6733): 271-5.
33. Na, X., Wu, G., Ryan, C.K., Schoen, S.R., di'Santagnese, P.A., Messing, E.M. *Overproduction of vascular endothelial growth factor related to von Hippel-Lindau tumor suppressor gene mutations and hypoxia-inducible factor-1 alpha expression in renal cell carcinomas.* J Urol 2003, 170(2, Pt. 1): 588-92.
34. Ito, Y., Sasaki, Y., Horimoto, M. et al. *Activation of mitogen-activated protein kinases/extracellular signal-regulated kinases in human hepatocellular carcinoma.* Hepatology 1998, 27(4): 951-8.
35. Villanueva, A., Newell, P., Chiang, D.Y., Friedman, S.L., Llovet, J.M. *Genomics and signaling pathways in hepatocellular carcinoma.* Semin Liver Dis 2007, 27(1): 55-76.
36. Calvisi, D.F., Ladu, S., Gorden, A. et al. *Ubiquitous activation of Ras and Jak/Stat pathways in human HCC.* Gastroenterology 2006, 130(4): 1117-28.
37. Semela, D., Dufour, J.F. *Angiogenesis and hepatocellular carcinoma.* J Hepatol 2004, 41(5): 864-80.
38. Schoenberger, J., Grimm, D., Kossmehl, P., Infanger, M., Kurth, E., Eilles, C. *Effects of PTK787/ZK222584, a tyrosine kinase inhibitor, on the growth of a poorly differentiated thyroid carcinoma: An animal study.* Endocrinology 2004, 145(3): 1031-8.
39. Viglietto, G., Maglione, D., Rambaldi, M. et al. *Upregulation of vascular endothelial growth factor (VEGF) and downregulation of placenta growth factor (PlGF) associated with malignancy in human thyroid tumors and cell lines.* Oncogene 1995, 11(8): 1569-79.
40. Bauer, A.J., Patel, A., Terrell, R. et al. *Systemic administration of vascular endothelial growth factor monoclonal antibody reduces the growth of papillary thyroid carcinoma in a nude mouse model.* Ann Clin Lab Sci 2003, 33(2): 192-9.
41. Casanovas, O., Hicklin, D.J., Bergers, G., Hanahan, D. *Drug resistance by evasion of antiangiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors.* Cancer Cell 2005, 8(4): 299-309.
42. Inoue, M., Hager, J.H., Ferrara, N., Gerber, H.P., Hanahan, D. *VEGF-A has a critical, nonredundant role in angiogenic switching and pancreatic beta cell carcinogenesis.* Cancer Cell 2002, 1(2): 193-202.
43. Abrams, T.J., Murray, L.J., Pesenti, E. et al. *Preclinical evaluation of the tyrosine kinase inhibitor SU11248 as a single agent and in combination with "standard of care" therapeutic agents for the treatment of breast cancer.* Mol Cancer Ther 2003, 2(10): 1011-21.
44. Baselga, J., Segalla, J.G., Roche, H. et al. *Sorafenib in combination with capecitabine: An oral regimen for patients with HER2-negative locally advanced or metastatic breast cancer.* J Clin Oncol 2012, 30(13): 1484-91.
45. Spano, J.P., Chodkiewicz, C., Maurel, J. et al. *Efficacy of gemcitabine plus axitinib compared with gemcitabine alone in patients with advanced pancreatic cancer: An open-label randomised phase II study.* Lancet 2008, 371(9630): 2101-8.
46. Hu-Lowe, D.D., Zou, H.Y., Grazzini, M.L. et al. *Nonclinical antiangiogenesis and antitumor activities of axitinib (AG-013736), an oral, potent, and selective inhibitor of vascular endothelial growth factor receptor tyrosine kinases 1, 2, 3.* Clin Cancer Res 2008, 14(22): 7272-83.
47. Olaussen, K.A., Commo, F., Tailler, M. et al. *Synergistic proapoptotic effects of the two tyrosine kinase inhibitors pazopanib and lapatinib on multiple carcinoma cell lines.* Oncogene 2009, 28(48): 4249-60.
48. Heinrich, M.C., Maki, R.G., Corless, C.L. et al. *Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor.* J Clin Oncol 2008, 26(33): 5352-9.
49. Lam, E.T., Ringel, M.D., Kloos, R.T. et al. *Phase II clinical trial of sorafenib in metastatic medullary thyroid cancer.* J Clin Oncol 2010, 28(14): 2323-30.
50. Zhang, W., Konopleva, M., Shi, Y.X. et al. *Mutant FLT3: A direct target of sorafenib in acute myelogenous leukemia.* J Natl Cancer Inst 2008, 100(3): 184-98.
51. Trudel, S., Li, Z.H., Wei, E. et al. *CHIR-258, a novel, multitargeted tyrosine kinase inhibitor for the potential treatment of t(4;14) multiple myeloma.* Blood 2005, 105(7): 2941-8.
52. Lee, S.H., Lopes de Menezes, D., Vora, J. et al. *In vivo target modulation and biological activity of CHIR-258, a multitargeted growth factor receptor kinase inhibitor, in colon cancer models.* Clin Cancer Res 2005, 11(10): 3633-41.
53. Chang, A.U. *TKI 258 Investigator's Brochure.* Novartis 2011.
54. Xin, X., Abrams, T.J., Hollenbach, P.W. et al. *CHIR-258 is efficacious in a newly developed fibroblast growth factor receptor 3-expressing orthotopic multiple myeloma model in mice.* Clin Cancer Res 2006, 12(16): 4908-15.
55. Lamont, F.R., Tomlinson, D.C., Cooper, P.A., Shnyder, S.D., Chester, J.D., Knowles, M.A. *Small molecule FGF receptor inhibitors block FGFR-dependent urothelial carcinoma growth in vitro and in vivo.* Br J Cancer 2011, 104(1): 75-82.
56. Sivanand, S., Pena-Llopis, S., Zhao, H. et al. *A validated tumorgraft model reveals activity of dovitinib against renal cell carcinoma.* Sci Transl Med 2012, 4(137): 137ra75.
57. Chen, K.F., Chen, H.L., Liu, C.Y., Tai, W.T., Ichikawa, K., Chen, P.J., Cheng, A.L. *Dovitinib sensitizes hepatocellular carcinoma cells to TRAIL and tigatuzumab, a novel anti-DR5 antibody, through SHP-1-dependent inhibition of STAT3.* Biochem Pharmacol 2012, 83(6): 769-77.
58. Tai, W.T., Cheng, A.L., Shiau, C.W. et al. *Dovitinib induces apoptosis and overcomes sorafenib resistance in hepatocellular carcinoma through SHP-1-mediated inhibition of STAT3.* Mol Cancer Ther 2012, 11(2): 452-63.
59. Huynh, H., Chow, P.K., Tai, W.M. et al. *Dovitinib demonstrates antitumor and antimetastatic activities in xenograft models of hepatocellular carcinoma.* J Hepatol 2012, 56(3): 595-601.
60. Lopes de Menezes, D.E., Peng, J., Garrett, E.N. et al. *CHIR-258: A potent inhibitor of FLT3 kinase in experimental tumor xenograft models of human acute myelogenous leukemia.* Clin Cancer Res 2005, 11(14): 5281-91.
61. Chase, A., Grand, F.H., Cross, N.C. *Activity of TKI258 against primary cells and cell lines with FGFR1 fusion genes associated with the 8p11 myeloproliferative syndrome.* Blood 2007, 110(10): 3729-34.
62. Azab, A.K., Azab, F., Quang, P. et al. *FGFR3 is overexpressed waldenstrom macroglobulinemia and its inhibition by dovitinib induces apoptosis and overcomes stroma-induced proliferation.* Clin Cancer Res 2011, 17(13): 4389-99.
63. Chang, A.U. *Dovitinib Investigator's Brochure.* 2012.
64. Kim, K.B., Chesney, J., Robinson, D., Gardner, H., Shi, M.M., Kirkwood, J.M. *Phase I/II and pharmacodynamic study of dovitinib (TKI258), an*

inhibitor of fibroblast growth factor receptors and VEGF receptors, in patients with advanced melanoma. Clin Cancer Res 2011, 17(23): 7451-61.

65. Sarker, D., Molife, R., Evans, T.R. et al. *A phase I pharmacokinetic and pharmacodynamic study of TKI258, an oral, multitargeted receptor tyrosine kinase inhibitor in patients with advanced solid tumors.* Clin Cancer Res 2008, 14(7): 2075-81.
66. Wang, X., Kay, A., Anak, O. et al. *Population pharmacokinetic/pharmacodynamic modeling to assist dosing schedule selection for dovitinib.* J Clin Pharmacol 2012.
67. http://www.clinicaltrials.gov/ct2/show/record/NCT01441414?term=angiopoietin&rank=11.