

## Inhibition of Src Family Kinases and Receptor Tyrosine Kinases by Dasatinib: Possible Combinations in Solid Tumors

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### Abstract

Dasatinib is a small molecule tyrosine kinase inhibitor that targets a wide variety of tyrosine kinases implicated in the pathophysiology of several neoplasias. Among the most sensitive dasatinib targets are ABL, the SRC family kinases (SRC, LCK, HCK, FYN, YES, FGR, BLK, LYN, and FRK), and the receptor tyrosine kinases c-KIT, platelet-derived growth factor receptor (PDGFR)  $\alpha$  and  $\beta$ , discoidin domain receptor 1 (DDR1), c-FMS, and ephrin receptors. Dasatinib inhibits cell duplication, migration, and invasion, and it triggers apoptosis of tumoral cells. As a consequence, dasatinib reduces tumoral mass and decreases the metastatic dissemination of tumoral cells. Dasatinib also acts on the tumoral microenvironment, which is particularly important in the bone, where dasatinib inhibits osteoclastic activity and favors osteogenesis, exerting a bone-protecting effect. Several preclinical studies have shown that dasatinib potentiates the antitumoral action of various drugs used in the oncology clinic, paving the way for the initiation of clinical trials of dasatinib in combination with standard-of-care treatments for the therapy of various neoplasias. Trials using combinations of dasatinib with ErbB/HER receptor antagonists are being explored in breast, head and neck, and colorectal cancers. In hormone receptor-positive breast cancer, trials using combinations of dasatinib with antihormonal therapies are ongoing. Dasatinib combinations with chemotherapeutic agents are also under development in prostate cancer (dasatinib plus docetaxel), melanoma (dasatinib plus dacarbazine), and colorectal cancer (dasatinib plus oxaliplatin plus capecitabine). Here, we review the preclinical evidence that supports the use of dasatinib in combination for the treatment of solid tumors and describe various clinical trials developed following a preclinical rationale. *Clin Cancer Res*; 17(17); 5546–52. ©2011 AACR.

### Background

Dasatinib is a small molecule tyrosine kinase inhibitor that was initially isolated as a dual SRC/ABL inhibitor (1). Its capability to block ABL has allowed its use in the treatment of chronic myelogenous leukemia (CML) and Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL; ref. 2). Dasatinib also inhibits other SRC family kinases (SFK), such as LCK, HCK, FYN, YES, FGR, BLK, LYN, and FRK (3). Moreover, dasatinib can block with high potency the kinase activity of certain receptor tyrosine kinases (RTK), such as c-KIT, c-FMS (the receptor of the macrophage colony stimulating factor), platelet-derived

growth factor receptors (PDGFR)  $\alpha$  and  $\beta$ , the discoidin domain receptor 1 (DDR1), and Ephrin receptors. The ample spectrum of kinase inhibitory properties of dasatinib, together with the demonstrated role of several of its target kinases in the pathophysiology of various neoplasias (Fig. 1), offers excellent opportunities for the development of dasatinib in those malignancies, especially in combination with standard-of-care treatments.

### Antitumoral actions of dasatinib

Dasatinib has been shown to inhibit cell duplication and promote cell death in different tumoral cells. In triple-negative breast cancer (TNBC) cells (4–6), in gastric (7), pancreatic (8), head and neck, and lung cell lines (9), and in myeloid leukemias (10), dasatinib inhibited cell duplication, causing G<sub>0</sub>-G<sub>1</sub> arrest. This effect has been attributed to an increase in p27 and p21, and a decrease in cyclin E, D1, and cyclin-dependent kinase 2 (CDK2) and retinoblastoma (Rb) phosphorylation status (9). Of note, in TNBC, dasatinib reduced the aldehyde dehydrogenase 1 (ALDH1)-positive cell population, indicating that this drug may be useful in decreasing the putative cancer stem cell population (11). In addition to causing an arrest of the cell cycle, dasatinib increased the sub-G<sub>0</sub> population, indicative of apoptosis (8, 9). Analogously, treatment of sarcoma cell lines with dasatinib triggered the cleavage of

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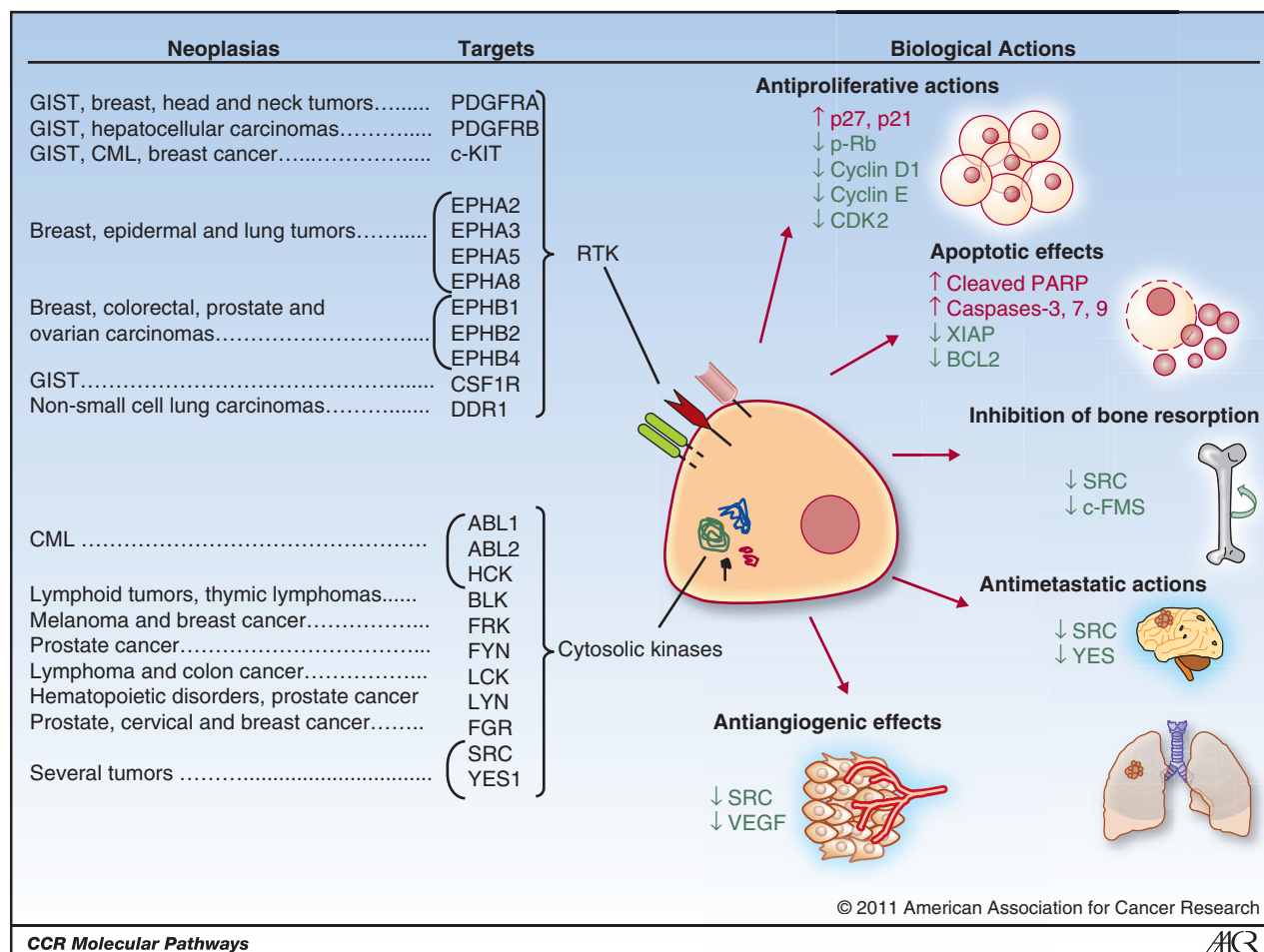


Figure 1. The most sensitive ( $IC_{50} < 1$  nmol/L) cytosolic and membrane targets of dasatinib, as well as the neoplastic disorders in which these targets are involved. The different biological actions and proteins that are affected by dasatinib are also shown. Green represents the proteins that decrease in amount or activity upon dasatinib treatment, and red are the proteins that dasatinib increases in amount or activity. GIST, gastrointestinal stromal tumor.

PARP, an indicator of caspase-mediated apoptosis, and decreased the level of X-linked inhibitor of apoptosis protein (XIAP), a protein that plays a key antiapoptotic role by directly inhibiting caspase-3, caspase-7, and caspase-9 (12). The apoptotic effect induced by dasatinib in these sarcoma models was likely due to inhibition of SRC (12). In chronic lymphocytic leukemia (CLL), in which SRC kinases play an important role in the signaling by the B-cell receptor, dasatinib increased reactive oxygen species and decreased B-cell lymphoma-2 (BCL2) and XIAP protein levels (13). The decrease in BCL2 was accompanied by derangement of the mitochondrial outer membrane, which in turn provoked mitochondrial depolarization, cytochrome-c release, and activation of the intrinsic apoptotic pathway, an action facilitated by decreased XIAP levels.

In addition to its effect on cell duplication and apoptosis, one of the important actions of dasatinib relates to inhibition of metastatic dissemination. Here the inhibitory action of dasatinib on SRC and SFKs seems to be the most relevant mechanism of action. SRC has been involved in the process

of metastasis, as it controls cell morphology, adhesion, migration, and invasiveness through its regulation of various signaling pathways downstream of several receptors or cytoskeleton components (14). In orthotopic mouse models of prostate cancer, dasatinib inhibited the activity of SRC and SFKs and reduced tumor growth and development of lymph node metastases (15). Analogously, dasatinib also decreased tumor growth and dissemination of pancreatic adenocarcinoma cells (16).

In addition, SRC regulates the tumor microenvironment, and this is particularly relevant in neoplastic diseases, such as prostate or breast cancers, which disseminate to the bone. Increased SRC activity has a net bone resorption result, as a consequence of inhibition of osteoblast generation, together with osteoclast stimulation (17). Treatment with dasatinib reverses the action of SRC and has, therefore, a dual effect on bone formation. On one hand, dasatinib induces osteoblast differentiation from bone marrow-derived mesenchymal stromal cells, therefore increasing bone formation (18, 19). On the other hand, dasatinib inhibits osteoclast activity,

likely through its inhibitory effect on SRC and Abl, also favoring bone formation (18, 20).

The bone remodeling properties of dasatinib may include additional targets. Thus, in a murine osteoclastogenesis assay, the inhibition of osteoclast activity by dasatinib was related to the inhibition of c-FMS (21).

### Dasatinib in combination

Although dasatinib has shown preclinical activity as a single agent, the fact that most antitumoral therapies are mainly based on combinations of drugs suggests that adequate use of dasatinib in the oncology clinic must be based on the finding of proper drug partners. In line with this idea, various preclinical studies have supported the use of dasatinib in combination with other antitumoral treatments.

Dasatinib, in combination with agents that target HER family RTKs, represents an attractive strategy for several reasons. First, several anti-HER strategies have reached the oncology clinic. Second, activated forms of SRC and HER kinases are frequent in cancer. In fact, HER receptors and SRC are overfunctional in approximately 70% of breast cancers (22). Third, SRC has been involved in signaling by HER receptors (23). Moreover, SRC has been reported to participate in resistance to trastuzumab, an anti-HER2 treatment used in the breast cancer clinic (24). In line with this, dasatinib has shown efficacy in HER2-overexpressing breast cancer models in combination with trastuzumab (25). Treatment with this drug combination caused cell cycle arrest and apoptosis. The drug combination decreased the amounts of RAD51, RAD1, and RAD54B, proteins that participate in the repair of DNA double strand breaks. As a consequence, this drug combination triggered a DNA damage response, as indicated by increased phosphorylation of histone H2AX, which may participate in the apoptotic response to the dasatinib plus trastuzumab combination (25). This effect was observed only with the drug combination, but not with either individual treatment, suggesting a synthetic lethality interaction between dasatinib-sensitive and trastuzumab-sensitive pathways. In another study, the combination of dasatinib with curcumin had a synergistic action on several TNBC cell lines, and this was attributed to their inhibitory effect on the epidermal growth factor receptor (EGFR, also termed HER1; ref. 6). SRC blockers also synergized with the anti-EGFR monoclonal antibody cetuximab in head and neck tumors (26). In colorectal carcinoma (CRC) cells, dasatinib sensitized to the action of cetuximab in cells bearing mutations in KRAS (27). This latter finding may have therapeutic implications, as mutations in KRAS are being used as criteria to exclude patients from the use of cetuximab or other anti-EGFR drugs (28).

The combination of dasatinib with an inhibitor (JSI-124) of STAT3 induced apoptosis in glioma cells (29). This combination triggered the release of cytochrome c and apoptosis-inducing factor (AIF) from the mitochondria to the cytosol and increased the cleavage of caspase 3 and PARP. Similarly, the dasatinib combination with

STAT3 inhibitors provoked viability loss of pancreatic cancer cells and decreased their migration and invasion (30). Dasatinib in combination with NVP-AEW541, an inhibitor of insulin-like growth factor-1 receptor (IGF-1R), also increased AIF and cytochrome-c release from the mitochondria in glioma cell lines (31). This increased apoptosis with the drug combination was attributed to AKT inhibition and activation of proapoptotic Bcl family members. In pancreatic cancer, the triple combination of dasatinib, erlotinib, and gemcitabine resulted in cooperative inhibition of migration and invasion through reduction of AKT, extracellular signal regulated kinase 1 and 2, focal adhesion kinase (FAK), and STAT signaling (32). Dasatinib and cisplatin have been shown to be highly active against TNBC (33) and human transitional cell carcinoma of the urothelium (34).

## Clinical-Translational Advances

### Markers of response to dasatinib

The identification of valid biomarkers that may predict the sensitivity of a tumor to dasatinib is important in designing treatments with this drug. One approach is the identification of active forms of the tyrosine kinases that are targets of dasatinib. The best example of this situation is offered by the *Bcr/Abl* translocation in CML, which renders the tumoral cells highly sensitive to the action of dasatinib. Other studies have also indicated that identification of active forms of the dasatinib target kinases may predict sensitivity to the drug. Thus, antibody-based cytometry techniques used in glioblastoma to screen for active kinases allowed the identification of SRC as a kinase frequently activated in those tumors (35). *In vitro* treatment with dasatinib had a strong antitumoral effect, supporting the validity of this approach (35). Some studies have attempted to define dasatinib sensitivity by analyzing global mRNA expression using microarrays to define patterns of gene expression linked to dasatinib sensitivity and/or resistance. Definition of an SRC oncogenic pathway signature (36) not only predicted sensitivity to dasatinib but also allowed others to uncover SRC as an important player in the metastatic spreading of breast cancer cells to the bone (37). Additional attempts to find markers of dasatinib sensitivity and/or resistance have been carried out by analyzing gene expression profiles in 23 breast cancer cell lines (38). That study identified a six-gene profile that predicted dasatinib sensitivity not only in breast but also in lung cancer cell lines. In addition, these authors also presented a gene expression signature related to dasatinib resistance (38). An SRC pathway activity index has also been defined to establish patients that may respond to dasatinib (39). The activity of SYK and phospholipase C $\gamma$ 2 (PLC $\gamma$ 2) may also correlate with sensitivity to dasatinib in CLL (13).

### Dasatinib combinations in solid tumors

The use of dasatinib in the clinic is not only supported by its success in the treatment of CML and ALL but also by

preclinical studies that have indicated that dasatinib inhibits tumor progression acting on the tumoral cell and its microenvironment. Thus, diseases in which bone metastases are frequent (e.g., breast or prostate tumors) could benefit from the addition of dasatinib to standard-of-care treatments. Moreover, dasatinib targets proteins that participate in signaling by kinases that play a pathogenic role in cancer (e.g., HER2 in breast cancer). The ample spectrum of biological functions affected by dasatinib (Fig. 1) offers interesting strategies to fight different types of tumors, especially using dasatinib in combination with standard-of-care treatments. Below, we comment on some representative clinical trials in diseases in which dasatinib use in combination may represent a rational strategy (Table 1).

**Breast cancer.** Different reasons justify the evaluation of dasatinib in breast cancer, including (i) SRC is overfunctional in a large proportion of breast cancer patients, (ii) SRC participates in signaling by HER receptors, (iii) dissemination of breast tumoral cells to the bone is frequent in this disease, and (iv) SRC has been linked to resistance to various therapies used in breast cancer. A recent study in which 615 breast cancer tumors were analyzed showed SRC activity to be tightly associated to the development of bone metastasis and late onset relapse to bone (37). In that study, and using preclinical breast cancer models, treatment with dasatinib alone reduced breast cancer bone metastases.

Breast cancer metastases to the bone are particularly frequent in estrogen receptor–positive (ER+) tumors. Interestingly, SRC plays a central role in the cross-talk between estrogen and androgen receptors (40, 41), and SRC expression and activity have been linked to resistance to anti-hormonal therapy (42, 43). These circumstances open the possibility of using dasatinib in the ER+ clinical setting (i) to overcome resistance to endocrine therapies, (ii) to prevent the appearance of such resistance, and (iii) to avoid metastatic spreading to the bone and/or to reduce the already disseminated cells. The NCT00371345 study was open to patients with both ER+ and/or HER2+ disease. Interestingly, response rates (RR) of 16% were observed in the ER+ cohort compared with 8% in the HER2+ cohort, suggesting the potential activity of dasatinib in ER+ tumors (44). Other ongoing studies are evaluating dasatinib in hormone receptor–positive breast tumors in association with hormone therapy, like letrozole or fulvestrant (NCT00696072 and NCT00903006). In hormone receptor–positive breast cancer, an ongoing trial is evaluating an antibody against IGF-1R with dasatinib and fulvestrant (NCT00903006). Although, it is known that IGF-1R is highly expressed and activated in hormone receptor–positive tumors, no preclinical evidence supports this combination.

Dasatinib could also be clinically useful for patients with tumors that overexpress HER2. In fact, preclinical evidence indicates that SRC associates to the intracellular region of HER2 and regulates the interaction between HER2 and HER3 (23). Moreover, SRC activity has been linked to resistance to trastuzumab (24). In this context, our data

showed that concomitant administration of dasatinib and trastuzumab produced a synergistic effect *in vitro* and in animal models, in which the drug combination provoked disappearance of the tumors (25). To explore the clinical relevance of these preclinical findings, a phase I and II study through the Spanish Breast Cancer Research Group Phase I Consortium (Net-GEICAM) testing weekly paclitaxel and trastuzumab, in addition to increasing doses of dasatinib (NCT01306942), is in progress. The phase II part of this study intends to identify potential signs of clinical activity.

Other studies are combining dasatinib with standard-of-care chemotherapy, such as capecitabine or paclitaxel, without selection of patients. Dasatinib and capecitabine have been tested in a phase I trial. Activity was limited, with only 13.5% of patients experiencing a partial response (PR; ref. 45). Dasatinib has also been explored in a phase I dose escalation trial in combination with weekly paclitaxel at 80 mg/m<sup>2</sup>. The dose selected for the phase II part was 120 mg (46). In this study, 25% of patients experienced PR.

**Prostate cancer.** In prostate cancer, SFK and FAK signaling are frequently overfunctional and have been linked to poor patient outcome, as well as resistance to anti-hormonal therapies (47). Treatment of prostate cancer cells with dasatinib results in inhibition of SFK activity, which causes reduction of the tumor mass accompanied by inhibition of metastatic spreading to the lymph nodes or to the bone (48). The latter effect may be related to the bone-protecting characteristic of dasatinib. In fact, in prostate cancer, tumored tibiae show a decrease in bone mineral density and trabecular bone volume (49, 50), which can be counteracted by dasatinib (51).

Dasatinib alone (52) and in combination (Table 1) with standard-of-care chemotherapies is being evaluated in prostate cancer. In a phase I and II study, 16 patients with castration-resistant prostate cancer were treated with escalating doses of every-3-weeks docetaxel and daily dasatinib. A cohort of 30 patients received docetaxel 75 mg/m<sup>2</sup> and dasatinib 100 mg daily. A total of 42% of patients experienced a PR, with 68% having PR or stable disease for more than 18 weeks (53). A prostate-specific antigen (PSA) response was present in almost half of the patients. Pleural effusion was diagnosed in only 7% of patients. An ongoing phase III trial is currently randomizing patients to receive docetaxel alone or with dasatinib 100 mg daily (NCT00744497).

**Melanoma.** Recent data suggest that the protein CUB-domain-containing protein 1 is highly expressed in melanoma and contributes to tumor metastasis through activation of SRC (54). Ongoing studies are evaluating dasatinib monotherapy in melanoma (55). Dasatinib, in addition to dacarbazine, is also being explored in this disease (56). The most common toxicities were hematologic, especially thrombocytopenia and neutropenia. Of 49 patients treated in this trial, 4 (8.2%) had PR and 25 (51.0%) had prolonged stabilization of disease. The rate of clinical benefit was 59.2%.

**Dasatinib combinations in other tumors.** Various preclinical studies support the use of dasatinib in CRC. A recent

**Table 1.** Selected clinical studies with dasatinib in combination

Tumor type	Tumor subtype	Selected phase II dose of dasatinib	Phase	Results	Agents in combination	Clinical trial	References
<b>Breast cancer</b>	ER+	100 mg daily	II	Ongoing	Letrozole	NCT00696072	
	ER+	—	I-II	Ongoing	Fulvestrant and an antibody against IGF-1R MK-0646	NCT00903006	
	HER2+	—	I-II	Ongoing	Paclitaxel and trastuzumab	NCT01306942	45
	No selection	100 mg daily	I	RR 13.5%	Capecitabine	NCT00452673	46
<b>Prostate cancer</b>	No selection	120 mg daily	I-II	PR 25%	Paclitaxel	NCT00820170	
	Chemotherapy-naïve CRPC	100 mg daily	I-II	PR 42%	Docetaxel	NCT00439270	53
<b>Melanoma</b>	Chemotherapy-naïve CRPC	100 mg daily	III	Ongoing	Prednisone + docetaxel	NCT00744497	
	Advanced melanoma	100 mg daily	I-II	PR 8.2%, clinical benefit 59.2%	Dacarbazine	NCT00597038	56
<b>Other tumor types</b>	NSCLC	—	I-II	Ongoing	Erlotinib	NCT00826449	59
	CRC	—	I-II	Ongoing	Bevacizumab and capecitabine and oxaliplatin	NCT00920868	
	CRC HNC	—	I	Ongoing	Cetuximab	NCT00835679	
			I-II	Ongoing	Cetuximab	NCT00882583	

Abbreviation: CRPC, castration-resistant prostate cancer.

study has linked the expression of lysyl oxidase to metastatic spreading of CRC (57). As this enzyme is regulated by SRC, the use of dasatinib in CRC could represent an interesting strategy to be tested. Also preclinical evidence links SRC with angiogenesis through an increased production of VEGF under hypoxic conditions (58). In this context, some ongoing studies are evaluating dasatinib in combination with antiangiogenic agents. An ongoing study is testing the combination of bevacizumab and dasatinib with capecitabine and oxaliplatin in metastatic CRC (NCT00920868). Other studies are evaluating the addition of dasatinib to cetuximab-based regimens in colorectal and head and neck cancers (HNC; NCT00835679 and NCT00882583). In the latter, preclinical studies have indicated that the combination of SRC inhibitors with anti-EGFR agents exerts a synergistic antitumoral action (26).

In lung cancer, SRC activity is elevated, and EGFR and SFK cooperation in sustaining tumor growth has been

reported (59). Dasatinib is currently under evaluation in combination with erlotinib in a phase I and II study (NCT00826449) in non-small cell lung cancer (NSCLC; ref. 59).

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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