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, PDGFRα and β, DDR1, c-FMS, and ephrin receptors. Dasatinib inhibits cell duplication, migration or invasion, and 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. This is particularly important in the bone, where dasatinib inhibits osteoclastic activity and favours 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) or 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.
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 leukaemia (CML) and Philadelphia chromosome positive acute lymphoblastic leukaemia (ALL) (2). Dasatinib also inhibits other SRC family kinases (SFK), such as LCK, HCK, FYN, YES, FGR, BLK, LYN, and FRK (3). Moreover, dasatinib can also block with high potency the kinase activity of certain receptor tyrosine kinases (RTKs) such as c-KIT, c-FMS (the receptor of the macrophage colony-stimulating factor), platelet-derived growth factor receptors (PDGFR) α and β, the discoidin domain receptor 1 (DDR1) or 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 (Figure 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), gastric, (7), pancreatic (8), head and neck and lung cell lines (9), or myeloid leukemias (10), dasatinib inhibited cell duplication, causing G0/G1 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 also increased the subG0 population, indicative of apoptosis (8, 9). Analogously, treatment of sarcoma cell lines with dasatinib triggered the cleavage of poly-ADP ribose polymerase (PARP), an indicator of caspase-mediated apoptosis, and decreased the level of X-linked inhibitor of apoptosis protein (XIAP), a protein who plays a key antiapoptotic role by directly inhibiting caspases-3, -7, and -9 (12). The apoptotic effect induced by dasatinib in these sarcoma models was likely due to inhibition of SRC (12). In chronic lymphocytic leukaemia (CLL) in which SRC kinases play an important role in the signalling 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 appears to be 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 signalling pathways downstream several receptors or cytoskeleton components (14). In orthotopic mouse models of prostate cancer, dasatinib inhibited the activity of SRC and SFKs, and reduced tumour growth and development of lymph node metastases (15). Analogously, dasatinib also decreased tumour growth and dissemination of pancreatic adenocarcinoma cells (16).

In addition, SRC regulates the tumour 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 favouring bone formation (18, 20).

The bone remodelling properties of dasatinib may also include other targets, in addition to SRC. 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**

While dasatinib has demonstrated 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 Human Epidermal Growth factor receptor (HER) family RTKs represents an attractive strategy for several reasons. First, because 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 signalling 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).
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 only observed 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) (6). SRC blockers also synergized with the anti-EGFR monoclonal antibody cetuximab in head and neck tumours (26). In colorectal carcinoma (CRC) cells, dasatinib sensitized to the action of cetuximab in cell 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 signal transducer and activator of transcription-3 (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, 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 pro-apoptotic 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 signalling (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 that 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 tumours (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/resistance. Definition of a 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/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). A SRC pathway activity index has
also been defined to establish patients that may respond to dasatinib (39). The activity of
SYK and phospholypase C\textgamma2 (PLC\textgamma2) may also correlate with sensitivity to dasatinib in
CLL (13).

**Dasatinib combinations in solid tumours**

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

**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 signalling 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 demonstrated 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 metastasis.

Breast cancer metastases to the bone are particularly frequent in estrogen receptor positive (ER+) tumours. 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 to use dasatinib in the ER+ clinical setting: (i) to overcome resistance to endocrine therapies, (ii) to prevent the appearance of such resistance, (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% was 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 homone receptor positive breast tumors in association with hormone therapy like letrozole or fulvestrant (NCT00696072; 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 tumours which 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 demonstrated 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 tumours (25). To explore the clinical relevance of these preclinical findings, a phase I-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 or 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) (45). Dasatinib has also been explored in a phase I dose escalation trial in combination with weekly paclitaxel at 80 mg/m². 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 signalling are frequently overfunctional, and have been linked to poor patient outcome as well as resistance to antihormonal therapies (47). Treatment of prostate cancer cells with dasatinib results in inhibition of SFK activity, which causes reduction of the tumour mass accompanied with 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 tumoured 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 I) with standard of care chemotherapies is being evaluated in prostate cancer. In a phase I-II study, 16 patients with castration-resistant prostate cancer were treated with escalating doses of every-3-week docetaxel and daily dasatinib. A cohort of 30 patients received docetaxel 75 mg/m² and dasatinib 100 mg daily. 42% of patients experienced a PR, with 68% having PR or stable disease for more than 18 weeks (53). A 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 suggests 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 dacarbacine is also being explored in this disease (56). The most common toxicities were hematological, especially thrombocytopenia and neutropenia. Of 49 patients treated in this trial, four (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 tumours**

Various preclinical studies support the use of dasatinib in CRC. A recent 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 vascular endothelial growth factor under hypoxic conditions (58).
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; NCT00882583). In the latter, preclinical studies have indicated that 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 tumour growth has been reported (59). Dasatinib is currently under evaluation in combination with erlotinib in a phase I-II study (NCT00826449) in non-small cell lung cancer (NSCLC) (59).
Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.
Table 1 Selected clinical studies with dasatinib in combination

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Tumor subtype</th>
<th>Selected phase II dose of Dasatinib</th>
<th>Phase</th>
<th>Results</th>
<th>Agents in combination</th>
<th>Clinical trail</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>ER+</td>
<td>100 mg daily</td>
<td>phase II</td>
<td>ongoing</td>
<td>letrozole</td>
<td>NCT00696072</td>
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<tr>
<td></td>
<td>ER+</td>
<td>-------</td>
<td>phase I-II</td>
<td>ongoing</td>
<td>fulvestrant and an antibody against IGF-1R MK-0646</td>
<td>NCT00903006</td>
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<tr>
<td></td>
<td>HER2+</td>
<td>-------</td>
<td>phase I-II</td>
<td>ongoing</td>
<td>paclitaxel and trastuzumab</td>
<td>NCT01306942</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No selection</td>
<td>100 mg daily</td>
<td>phase I</td>
<td>RR 13.5%</td>
<td>capcitabine</td>
<td>NCT00452673</td>
<td>(45)</td>
</tr>
<tr>
<td></td>
<td>No selection</td>
<td>120 mg daily</td>
<td>phase I-II</td>
<td>PR 25%</td>
<td>paclitaxel</td>
<td>NCT00820170</td>
<td>(46)</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>chemotherapy-naive CRPC</td>
<td>100 mg daily</td>
<td>phase I-II</td>
<td>PR 42%</td>
<td>docetaxel</td>
<td>NCT00439270</td>
<td>(53)</td>
</tr>
<tr>
<td></td>
<td>chemotherapy-naive CRPC</td>
<td>100 mg daily</td>
<td>Phase III</td>
<td>ongoing</td>
<td>prednisone + docetaxel</td>
<td>NCT00744497</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>advanced melanoma</td>
<td>100 mg daily</td>
<td>Phase I-II</td>
<td>PR 8.2%</td>
<td>Clinical benefit 59.2%</td>
<td>Dacarbazine</td>
<td>NCT00597038 (56)</td>
</tr>
<tr>
<td>Other tumor types</td>
<td>NSCLC</td>
<td>-------</td>
<td>Phase I-II</td>
<td>ongoing</td>
<td>erlotinib</td>
<td>NCT00826449</td>
<td>(59)</td>
</tr>
<tr>
<td></td>
<td>CRC</td>
<td>-------</td>
<td>Phase I-II</td>
<td>ongoing</td>
<td>bevacizumab and capcitabine and oxaliplatin</td>
<td>NCT00920868</td>
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<tr>
<td></td>
<td>CRC</td>
<td>-------</td>
<td>Phase I</td>
<td>ongoing</td>
<td>cetuximab</td>
<td>NCT00835679</td>
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<td></td>
<td>HNC</td>
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<td>Phase I-II</td>
<td>ongoing</td>
<td>cetuximab</td>
<td>NCT00882583</td>
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</table>
References


**Figure 1.** The figure shows the most sensitive (IC50 < 1 nM) 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 in red are shown the proteins that dasatinib increases in amount or activity.
<table>
<thead>
<tr>
<th>Neoplasias</th>
<th>Targets</th>
<th>Biological Actions</th>
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</thead>
<tbody>
<tr>
<td>GIST, breast, head and neck tumors</td>
<td>PDGFRA</td>
<td>Antiproliferative actions</td>
</tr>
<tr>
<td>GIST, hepatocellular carcinomas</td>
<td>PDGFRB</td>
<td></td>
</tr>
<tr>
<td>GIST, CML, breast cancer</td>
<td>KIT</td>
<td></td>
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<tr>
<td>Breast, epidermal and lung tumors</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>EPHA2, EPHA3, EPHA5, EPHA8</td>
<td>Apoptotic effects</td>
</tr>
<tr>
<td>Breast, colorectal, prostate and ovarian carcinomas</td>
<td>EPHB1, EPHB2, EPHB4</td>
<td></td>
</tr>
<tr>
<td>GIST</td>
<td></td>
<td></td>
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<tr>
<td>Non-small cell lung carcinomas</td>
<td>CSF1R, DDR1</td>
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<td>CML</td>
<td></td>
<td></td>
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<tr>
<td>Lymphoid tumors, thymic lymphomas</td>
<td>ABL1, ABL2, HCK</td>
<td>Antimetastatic actions</td>
</tr>
<tr>
<td>Melanoma and breast cancer</td>
<td>BLK</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>FRK</td>
<td></td>
</tr>
<tr>
<td>Lymphoma and colon cancer</td>
<td>LCK</td>
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<td>Hematopoietic disorders, prostate cancer</td>
<td>LYN</td>
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<tr>
<td>Prostate, cervical and breast cancer</td>
<td>FGR, SRC, YES1</td>
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</tr>
<tr>
<td>Several tumors</td>
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</tr>
</tbody>
</table>

**Antiproliferative actions**
- ↑ p27, p21
- ↓ p-Rb
- ↓ Cyclin D1
- ↓ Cyclin E
- ↓ CDK2

**Apoptotic effects**
- ↑ Cleaved PARP
- ↑ Caspases-3, 7, 9
- ↓ XIAP
- ↓ BCL2

**Inhibition of bone resorption**
- ↓ SRC
- ↓ c-FMS

**Antimetastatic actions**
- ↓ SRC
- ↓ YES

**Antiangiogenic effects**
- ↓ SRC
- ↓ VEGF
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