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# The use of single-agent dasatinib in molecularly unselected non-small-cell lung cancer patients

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## Abstract

A Phase II study of the Src family kinase (SFK) inhibitor dasatinib was recently reported in molecularly unselected patients with metastatic NSCLC. SFK inhibition has a strong rationale as a clinical strategy in NSCLC. The reviewed study unfortunately showed disappointing activity as monotherapy in this molecularly unselected patient cohort and toxicity in terms of pleural effusion was problematic. Therefore, dasatinib as monotherapy in this setting does not appear promising. Nonetheless, the reviewed study may be used in conjunction with other studies of dasatinib in NSCLC to identify patients more likely to benefit from dasatinib either as monotherapy or in combination with other agents. Future studies of dasatinib in NSCLC should examine the agent in combination with EGFR inhibitors and/or cytotoxic chemotherapies.

### Keywords

clinical trial; dasatinib; NSCLC; small molecules

## 1. Introduction

Based on preclinical work suggesting the importance of the Src family kinases (SFKs), in NSCLC [1], a recent Phase II study of the SFK inhibitor dasatinib has been conducted in patients with metastatic NSCLC [2]. SFKs have been demonstrated to have an important role in many oncologic functions in human tumors, including proliferation, motility, migration, survival and angiogenesis [3]. In particular, in preclinical studies, an interaction between SFK inhibition and cell survival has been noted in EGFR-dependent NSCLC cell lines [4–6]. The recent identification of new promising targets in NSCLC that can be manipulated via targeted therapy, such as EML4-ALK [7], has further demonstrated that targeted therapy, in properly selected patients, can result in impressive clinical efficacy [8,9], with minimal toxicity as compared to traditional cytotoxic chemotherapy. Johnson *et al.* [2], therefore, sought to examine the efficacy of dasatinib in a molecularly unselected



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group of metastatic NSCLC patients, while attempting to identify biomarkers that could help to refine a patient population that may benefit from SFK inhibition.

## 2. Study design

The primary objective of the trial was to determine the efficacy of dasatinib in metastatic NSCLC, as measured by progression-free survival at 12 weeks. Thirty-four patients with radiographically measurable, metastatic NSCLC and an Eastern Cooperative Oncology Group performance status of 0 – 1 were included. Any patient who had previously received cytotoxic chemotherapy for metastatic disease was not allowed to enroll. Patients received oral dasatinib daily until disease progression or unacceptable toxicity was observed. Secondary objectives included the novel end point of metabolic response, as measured by 6- and 12-week positron emission tomography (PET)-CT standardized uptake value (SUV) as compared to baseline PET-CT SUV. Disease response was also measured as Response Evaluation Criteria in Solid Tumors (RECIST) criteria, and partial response (PR) plus stable disease (SD) at 12 weeks was deemed to represent the disease control rate. Relationships between clinical response to dasatinib and biomarkers were also analyzed, including EGFR mutational status, activated SFK expression, EGFR copy number, changes in serum cytokines and phosphorylated Src levels in platelets.

## 3. Key results

- The initial dosing of dasatinib was 100 mg twice a day. Because of significant fatigue and pleural effusions seen in the first 22 patients, the remaining patients received 100 mg in the morning and 50 mg in the evening.
- The most common grade 3 toxicity was dyspnea and pleural effusions were problematic. Over a third of patients who received the higher starting dose (100 mg twice a day) developed new pleural effusions. Nineteen (56%) patients had dasatinib either discontinued or held due to dyspnea and/or pleural effusions. Certainly, underlying COPD and thoracic malignancy contributed to these observations.
- The median duration of dasatinib treatment was 1.36 months. All patients discontinued dasatinib, with the majority stopping secondary to progressive disease, which occurred at a disappointing median of 1.36 months.
- The overall disease control rate (PR + SD) was 43% at 12 weeks, with only one patient showing PR. Four (12%) patients had SD for > 6 months. The observed activity of dasatinib appeared inferior to standard first-line cytotoxic chemotherapy regimens for metastatic NSCLC.
- Because of the early progressive disease and resultant dasatinib discontinuation, this unfortunately meant that > 50% of patients would not have been on active dasatinib at the planned 6-week PET-CT for measuring metabolic response. Indeed, only 21 of 34 patients underwent the protocol-specified metabolic response assessment. Seven (21%) patients had partial metabolic response, while patients with progressive metabolic disease tended to have a shorter time to disease progression as determined by RECIST criteria.
- Biomarker studies and pharmacodynamic measurements were not successful at demonstrating a patient population more likely to show benefit from dasatinib.
- Median overall survival was 11.4 months, which is in line with expectations in the first-line setting for patients with metastatic NSCLC [10], probably indicating that

patients who progressed on dasatinib went on to receive standard cytotoxic chemotherapy (these details were not outlined in the manuscript).

- One patient had a striking and durable response and is still free of disease 3 years later. He has never received therapy other than dasatinib.

## 4. Expert opinion

The highlighted study was an ambitious endeavor that deserves credit for its thoughtful design. By studying the Src inhibitor dasatinib in patients with newly diagnosed metastatic NSCLC, the investigators were able to perform many correlative studies that may have not been feasible in a more advanced group of patients who had previously progressed through cytotoxic chemotherapy. Furthermore, tissue biologic parameters had been collected in close temporal fashion to dasatinib administration. It is well known that NSCLC tumor biology can change following administration of cytotoxic chemotherapies, and this confounder was, therefore, avoided in their correlative analyses. Additionally, the use of metabolic response via PET-CT, while not standard via the recently updated RECIST criteria [11], allowed for an assessment of therapeutic efficacy that may be more sensitive than standard response criteria. This approach may warrant incorporation into future studies investigating molecularly targeted therapies, where cytostatic effects may predominate (as opposed to cytotoxic effects).

While the clinical activity of dasatinib was disappointing and correlative studies in this small cohort were not able to identify a patient subpopulation for potential future studies, dasatinib has strong rationale for study in NSCLC. In considering its future, a brief review of the timeline of EGFR inhibitors in NSCLC may be considered, as it illuminates the challenges, and ultimate successes, in developing molecularly targeted therapies in NSCLC. Based on promising Phase II studies of erlotinib [12] and gefinitib [13], Phase III studies were undertaken, which initially failed to identify a benefit of these agents in unselected patient populations [14–16]. However, with the gained clinical experience, subclasses of patients likely to benefit from these therapies were identified [17,18], and subsequent studies performed in enriched patient populations have indeed identified a clinical niche for these molecularly targeted agents [9,19].

It is premature to conclude whether dasatinib (and SFK inhibition) may or may not experience a similar trajectory in NSCLC therapy. Preclinical studies suggest that the utility of SFK inhibition is magnified in the presence of cytotoxic chemotherapy [20] or EGFR inhibition, and initial clinical studies investigating such combinations have shown promise [21]. Thus, the study by Johnson *et al.* [2] represents an early chapter in the story of SFK inhibition in NSCLC.

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