Phase II Trial of Dasatinib for Patients with Acquired Resistance to Treatment with the Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Erlotinib or Gefitinib

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Introduction: Dual inhibition of *SRC*- and *EGFR*-dependent pathways may overcome acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) for patients with lung adenocarcinoma with *EGFR* mutations. The *SRC* inhibitor dasatinib demonstrates antitumor activity in gefitinib-resistant cells lines and xenografts. Dasatinib is tolerable for patients with advanced non-small cell lung cancer, and in combination with erlotinib.

Methods: We conducted this phase II study of dasatinib 70 mg twice daily in patients with *EGFR*-mutant lung adenocarcinoma and acquired resistance to EGFR-TKIs. After a protocol amendment based on evolving data about both drugs, patients received dasatinib at a dose of 100 mg daily with continued erlotinib after developing acquired resistance. Enrolled patients either harbored an activating mutation in *EGFR* or experienced clinical benefit with single-agent erlotinib or gefitinib, followed by RECIST documented progression while being treated with an EGFR-TKI.

Results: Twenty-one patients were enrolled, 9 under the original trial design and 12 after the protocol amendments. We observed no complete or partial responses (0% observed rate, 95% confidence interval: 0–18%). The median time to progression was 0.5 months (range, 0.2–1.8 months) in patients treated with dasatinib and 0.9 months (range, 0.4–5 months) for patients treated with dasatinib and erlotinib in combination. Pleural effusions and dyspnea were frequent toxicities.

Conclusions: Dasatinib has no activity in patients with *EGFR*-mutant lung adenocarcinoma with acquired resistance to erlotinib and gefitinib.

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Seventy percent of patients with lung adenocarcinoma harboring mutations in the epidermal growth factor receptor (*EGFR*) gene experience a partial response when treated with EGFR tyrosine kinase inhibitors (TKIs) erlotinib or gefitinib.[1] However, the majority of patients progress within 17 months of the start of the treatment.[2] At least 50% of lung cancer patients with acquired resistance to erlotinib or gefitinib develop a secondary T790M mutation within *EGFR*, and another 10 to 15% of patients demonstrate *MET* amplification.[3–5] Therapies directed against these mechanisms of acquired resistance are desperately needed.

SRC is a nonreceptor tyrosine kinase that demonstrates increased protein levels in *EGFR*-dependent tumors. *SRC* and *EGFR* are proteins capable of mutual phosphorylation that share downstream effectors such as phosphatidylinositol 3-kinase/PTEN/Akt and *STAT* proteins.[6] Because of these functional associations, *SRC* kinase has been proposed as a target to overcome acquired resistance in *EGFR*-mutant tumors.

Preclinical models demonstrate *EGFR*-mutant cell lines containing either L858R (H3255) or exon 19 deletions (PC9 or HCC827) undergo apoptosis when treated with the *SRC* inhibitor dasatinib.[7] Gefitinib-resistant adenocarcinoma cells with T790M (PC9/ZD) or *MET* amplification (HCC827 GR5) undergo cell death when treated with dasatinib.[8] Dasatinib also inhibits tumor growth in HCC827 GR5 nude mouse xenografts.[8] Dasatinib has been studied in patients with advanced solid tumors, with pleural effusions dose-limiting.[9] Dasatinib can be combined with erlotinib in unselected patients with advanced non-small cell lung cancer (NSCLC).[10]

Given its preclinical rationale and early clinical trial results, we conducted a phase II study of dasatinib in patients with *EGFR*-mutant lung adenocarcinoma and acquired resistance to the EGFR-TKIs erlotinib and gefitinib.

PATIENTS AND METHODS

Patients with lung adenocarcinoma meeting consensus criteria for acquired resistance were eligible.[11] All patients

agreed to undergo a repeat tumor biopsy. This protocol was reviewed and approved by the Institutional Review Board at Memorial Sloan-Kettering Cancer Center.

Initial Study Design

Seven days after discontinuing erlotinib or gefitinib therapy, patients began dasatinib at a dose of 70 mg twice daily. Patients were evaluated by computed tomography scan at 4 weeks, 8 weeks, and at 8-week intervals. Modified Response Evaluation Criteria in Solid Tumors (version 1.1) were used to assess response. Toxicities were graded using the National Cancer Institute Common Terminology Criteria of Adverse Events (version 3.0).

A Simon two-stage design was employed to calculate an initial sample size of 12. Cohort expansion to 37 patients was planned if one or more partial responses were observed. If 4 or more of the first 12 patients developed grade 3 or 4 pleural effusions, the trial would be stopped.

Amended Design

Coincident with the start of this trial, we observed that patients with acquired resistance who discontinued EGFR-TKIs experienced symptomatic deterioration and accelerated tumor growth with increased [18^F]-fluorodeoxyglucose (FDG) avidity on positron emission tomography scans.[12] After restarting erlotinib or gefitinib in these patients, tumors decreased in size and SUV_{max} on repeat studies, and tumor-related symptoms improved. Given these observations, we now recommend continued erlotinib in patients with acquired resistance while also adding second-line treatment agents and amended this protocol to allow patients to continue erlotinib in addition to beginning dasatinib. In addition, new data indicated that dasatinib 100 mg daily provided similar efficacy with less pleural effusions when used to treat patients with chronic myelogenous leukemia (CML),[13] and we further amended this trial to allow a dose of dasatinib 100 mg daily.

Mutational Analysis

Before initiating dasatinib, all patients underwent tumor biopsies, preferably at a site of growing or new disease. Genomic DNA was extracted from tumor specimens, and all *EGFR* mutations (exon 19 deletions, L858R and T790M substitutions) were identified by mutation-specific polymerase chain reaction-based methods.[14] Tumor specimens were analyzed for *MET* amplification using dual-color fluorescent in situ hybridization with a *MET*-specific gene probe.[5] *MET* amplification was defined as having a *MET*:CEP7 ratio of >2:1.

RESULTS

Dasatinib 70 mg Twice Daily

Nine patients were enrolled under the original trial design. The median age was 68 years, and 66% of patients were women (Table 1). Similar numbers of patients in this cohort harbored exon 19 deletions and L858R mutations in their tumors. One patient had insufficient tissue for analysis (Table 2).

TABLE 1. Patient Characteristics

Characteristic	Dasatinib 70 mg Twice Daily (n = 9)	Dasatinib 100 mg Daily + Erlotinib (n = 12)
Age, median (range)	68 (35–80)	60 (51–73)
Female/male	6/3	7/5
Smoking history		
Never	7	8
Former	1	3
Current	1	1
KPS (median)	80	80
Months (median) treated with EGFR-TKI before developing acquired resistance	16 (8–102)	21 (12–49)

KPS, Karnofsky performance score; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor.

TABLE 2. Molecular Studies of Tumor Specimens

	Dasatinib 70 mg Twice Daily (n = 9)	Dasatinib 100 mg Daily + Erlotinib (n = 12)
Primary *EGFR* mutations		
Exon 19 deletion	4	10
L858R	4	2
Unable to be tested[a]	1	0
Molecular abnormalities found at the time of developing acquired resistance		
T790M + Exon 19 del	2	8
T790M + L858R	2	0
T790M not found + Exon 19 del	2	2
T790M not found + L858R	1	2
T790M unable to be tested[a]	2	0
MET amplification present	0	0
MET amplification absent	4	7
MET amplification unable to be tested[a]	5	5

[a] Unable to be tested due to insufficient tumor tissue.

Patients were treated for a median of 16 months with primary EGFR-TKIs before developing acquired resistance (Table 1). When rebiopsied at the time of study enrollment, 44% (4/9) of patients had developed T790M acquired resistance mutations; none of the patients with adequate tissue for fluorescent in situ hybridization testing exhibited *MET* amplification (0/4 tested) (Table 2).

There were no complete or partial responses observed (0%, 95% confidence interval: 0–34%). All patients progressed within 2 months of starting dasatinib. The median time until progression was 0.5 months (range, 0.2–1.8 months). The median overall survival was 13 months.

The combination of rapid disease progression among these initial nine patients, the majority (6/9) of whom developed pleural effusions, prompted revisions to our protocol design, although still 3 patients away from its required sam-

