Original Study

A Phase II Trial of Saracatinib, an Inhibitor of src Kinases, in Previously-Treated Advanced Non–Small-Cell Lung Cancer: The Princess Margaret Hospital Phase II Consortium

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Abstract

Treatment options for advanced non–small-cell lung cancer (NSCLC) after failure of platinum-based chemotherapy are limited. Dysregulated src kinases may play a role in the malignant phenotype. This 2-stage phase II study evaluated saracatinib, an inhibitor of src kinases in this patient population, and responses were observed, including in a patient with an activating epidermal growth factor receptor (*EGFR*) mutation. Future studies of this class of agents in molecular subtypes of NSCLC are warranted.

Background: The src family of kinases may play a role in the malignant phenotype through effects on migration, motility, adhesion and proliferation. The activity of saracatinib, an orally available inhibitor of src kinases, was evaluated in patients with advanced, platinum-pretreated NSCLC. **Patients and Methods:** Eligible patients with advanced NSCLC of any histologic subtype and who had obtained a best response to prior platinum-based chemotherapy of at least stable disease received saracatanib 175 mg orally daily in a 28 day cycle. The primary end point was the proportion of patients progression-free after 4 cycles (16 weeks) of therapy; 8 such patients of 32 evaluable were required to deem the therapy active. Immunohistochemistry for src expression was performed on archival tissue from enrolled patients. **Results:** Thirty-seven patients received a median of 2 cycles (range, 1–14) each. Six of 31 evaluable patients were progression-free at 16 weeks. Two partial responses were observed, lasting 3.7 and 14.6 months; 1 responder had an *EGFR* exon 19 deletion. An additional 4 patients had stable disease for at least 4 cycles. The median progression-free and overall survival times were 1.8 and 7.6 months. No correlation between src protein expression and outcome was observed. **Conclusions:** There may be a subset of saracatinib-responsive NSCLC that is currently molecularly undefined. Further studies of this agent in a population preselected for target mutations that potentially relevant to src pathways, such as *EGFR*, should be considered.

Clinical Lung Cancer, Vol. 15, No. 1, 52-7
Keywords: Biomarker, Non–small cell, Src inhibitor, Systemic therapy

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Submitted: May 3, 2013; Revised: Jun 28, 2013; Accepted: Aug 6, 2013; Epub: Oct 26, 2013

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Introduction

Non–small-cell lung cancer (NSCLC) is the most common cause of cancer death in North America. After first-line platinum-doublet combination chemotherapy, those patients who do not receive maintenance therapy may be eligible to receive additional treatment at the time of disease progression. Standard second-line chemotherapies are docetaxel[1] and pemetrexed.[2] Both these agents, in histology-unselected populations, lead to an objective response rate of less than 10%, a median survival of approximately 8

1525-7304/$ - see frontmatter
http://dx.doi.org/10.1016/j.clc.2013.08.001

months, and a median progression-free survival of 3 months. Although some patients benefit from these agents, a large proportion does not, and more effective therapies are needed.

The src family of nonreceptor tyrosine kinases consists of 9 homologues, some of which (such as src and fyn) are ubiquitously expressed,[3] and which integrate a number of cellular signaling pathways.[4] Increased src tyrosine kinase activity in tumors is felt to contribute to the malignant phenotype, mediating processes such as migration, adhesion and proliferation, and src expression has been noted to increase as the disease progresses.[5] Thus inhibition of dysregulated src may be a relevant therapeutic strategy.

Saracatinib (AZD0530, AstraZeneca, Macclesfield, UK), is an orally available inhibitor of multiple members of the src family of kinases, with IC_{50} values in the low nanomolar range. Additionally, it has moderate activity against Abl (IC_{50} 30 nmol/L) and wild-type epidermal growth factor receptor (EGFR) tyrosine kinase (66 nmol/L), and more potent activity against certain mutated EGFR variants, such as L858R (5 nmol/L).[6] It has demonstrated antitumor activity in preclinical models, predominantly by greater inhibition of cancer cell motility rather than inhibition of cell growth.[6] In lung cancer models, saracatinib significantly impaired cell migration and invasion.[7] The recommended phase II dose from the phase I study[8] was 175 mg/d. The most common toxicities observed in the dose-finding study were asthenia, diarrhea and anemia; 2 episodes of pneumonitis were observed which were deemed possibly related to study therapy. This trial evaluated saracatinib in patients with previously-treated NSCLC. It was felt that saracatinib would have antimetastatic and cytostatic, but not necessarily cytotoxic, activity. Because it was unclear whether, as a single-agent, saracatinib would induce objective responses, the proportion of patients progression-free at 16 weeks was chosen as the primary end point. This magnitude of disease stabilization was felt by the investigators to be clinically relevant in this setting.

Patients and Methods

Patients

This open-label, multicenter phase II study (NCT00638937) evaluated the activity of saracatinib in patients who had previously obtained at least stabilization of disease with first-line platinum-based combination chemotherapy for advanced, incurable NSCLC. Chemotherapy administered as adjuvant treatment or as part of a chemoradiation regimen for locally-advanced disease counted as treatment for advanced disease if the patient relapsed within 12 months of this therapy. Patients who were retreated with platinum-based chemotherapy more than 1 year after potentially curative therapy were also eligible.

Eligible patients were $\geq$ 18 years of age, had incurable, histologically or cytologically proven NSCLC of any histology, and were Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; had a life expectancy $\geq$ 12 weeks; and had radiologically measurable disease and adequate hematologic (leukocytes, $\geq 3.0 \times 10^9$/L; granulocytes, $\geq 1.5 \times 10^9$/L; platelets, $\geq 100 \times 10^9$/L; hemoglobin, > 9 g/dL) and biochemical (bilirubin $\leq$ 1.5 upper institutional limit of normal [ULN]; aspartate aminotransferase and alanine aminotransferase $\leq 2.5 \times$ ULN or $\leq 5 \times$ ULN in the presence of liver metastases; serum creatinine $\leq 1.5 \times$ ULN or creatinine clearance of $\geq$ 50 mL/min if serum creatinine is > ULN; urine protein creatinine ratio $\leq$ 1.0 or 24-h urine protein excretion < 1000 mg) parameters.

Patients were ineligible if they had progressed during first-line platinum-doublet chemotherapy or had received more than 1 line of systemic therapy for advanced disease, including epidermal growth factor receptor (EGFR) inhibitors. Prior chemotherapy or radiotherapy was completed at least 4 weeks before study entry (6 weeks for nitrosoureas or mitomycin), and patients must have recovered from all toxic effects; no more than 40% of bone marrow may have been radiated. Other exclusion criteria included the following: untreated or symptomatic brain metastases requiring corticosteroids; QTc interval of > 460 ms; impaired ability to swallow, retain, or absorb the saracatinib tablets; HIV positivity on combination antiretroviral agents; pregnancy or lactation; poorly controlled hypertension (systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg); or cardiac dysfunction, including symptomatic heart failure, unstable angina, or cardiac arrhythmia or a history of ischemic heart disease including myocardial infarction.

This study was approved by the research ethics boards of the participating institutions. All patients provided written informed consent. The trial was conducted in accordance with Good Clinical Practice guidelines.

Objectives and Statistical Considerations

The primary end point was to determine the rate of disease control (ie, lack of disease progression, a combined rate of objective complete and partial responses, and stable disease as determined by Response Evaluation Criteria in Solid Tumours (RECIST) 1.0[9]) for at least 4 cycles (16 weeks) of therapy. Secondary objectives were to assess objective response rate; the rate of stable disease; duration of response or stabilization of disease; progression-free, median, and overall survival rates; and safety and tolerability of this treatment in this population. Exploratory correlative studies included the assessment of pretreatment intratumoral levels of src, activated src [Y419 phospho-src (p-src)] and c-terminal src kinase (csk) in archival tumor biopsy specimens and their potential relationship with treatment outcomes.

A 2-stage design was used for determination of sample size.[10] The agent would be declared inactive if the rate of disease control at 4 cycles was $\leq$ 15% and active if $\geq$ 35%. For stage I, if at least 3 of 17 response-evaluable patients were progression-free at cycle 4, then accrual would continue. For stage II, an additional 15 response-evaluable patients were to be accrued, and the treatment deemed active if 8 or more of 32 patients were progression-free at cycle 4. With this design, the true α error was set at 0.091 and the true β set at 0.095.

Study Therapy

Saracatinib, provided by the Cancer Therapy Evaluation Program of the National Cancer Institute (Bethesda, MD), was administered at 175 mg orally once daily (as one 125-mg and one 50-mg tablet); cycle length was 28 days. As many as 2 dose reductions (to 125 mg or 100 mg) for toxicity were permitted. In general, for most grade-3 or higher nonhematologic or grade-4 hematologic toxicities lasting more than 5 days, saracatinib was held until resolution to less than or equal to grade 2 then reduced 1 dose level. If a patient developed new or worsening dyspnea or cough or new pulmonary radiologic

abnormality which could not categorically be clinically attributed to another cause, saracatinib was interrupted, and if a high resolution CT scan of the thorax demonstrated interstitial lung disease, then saracatinib was discontinued permanently. In the absence of unacceptable toxicity, intercurrent illness that prevented its administration, or patient request to discontinue, saracatinib was continued until disease progression.

No concomitant anticancer therapy was permitted. Use of certain CYP3A4 active agents (eg, ketoconazole, clarithromycin, diltiazem, lovostatin) was prohibited.

Pretreatment and on-Treatment Assessments

Within 7 days of registration, patients underwent a complete history and physical examination, an assessment of ECOG PS, pulmonary function tests, urinary protein determination, and analyses of hematologic and biochemical parameters, with a urine pregnancy test performed in women of child-bearing potential. Radiologic assessments of sites of disease and an electrocardiographic examination were performed within 28 days.

Patients were seen by the investigator every 2 weeks for the first cycle, then every 4 weeks thereafter. For the first cycle, hematology, biochemistry, and urinalysis were repeated weekly, then on day 1 of every cycle. Pulmonary function tests were repeated every 2 weeks for the first cycle and thereafter only if imaging studies suggested abnormal findings consistent with pneumonitis.

Toxicity was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 [Bethesda, MD]. Response was assessed every 8 weeks (every 2 cycles) by RECIST 1.0.[9] Response on study was determined by the investigator, but an independent radiologic review of all patients meeting the primary end point was performed.

Table 1 Patient Characteristics

Characteristic	No. of Patients
Enrolled patients, n	37
Ineligible	1
Assessable for primary end point	31
Assessable for toxicity	37
Men/women, n/n	9/28
Median age, years (range)	65 (33–78)
ECOG performance status	
0	17
1	19
2	1
Cancer type	
Adenocarcinoma	19
Squamous carcinoma	9
NSCLC, not otherwise specified	8
Cervical carcinoma[a]	1
Race	
White	34
East Asian	2
Unknown	1
Smoking status	
Current smoker	3
Ex-smoker	21
Never smoked	5
Unknown	8

Abbreviation: ECOG = Eastern Cooperative Oncology Group.
[a]Patient ineligible; included in safety assessments.

Correlative Studies

Optional archival tumor tissue was collected from consenting patients enrolled to this trial. Immunohistochemistry (IHC) for intratumoral src, p-src and csk was performed. Formalin-fixed paraffin-embedded archival tissue was cut at 4-μm thickness. The sections were dried at 60°C overnight. Immunostaining was performed on a Ventana Benchmark XT fully automated slide preparation system using the iVIEW DAB detection kit and the following antibodies: monoclonal rabbit anti-src (36D10) (#2109, 1:2000 dilution; Cell Signaling Technology [Danvers, MA]), polyclonal rabbit anti-phospho-src family (Tyr416) (#2101, 1:25 dilution; Cell Signaling Technology), monoclonal rabbit anti-csk (C74C1) (#4980, 1:25 dilution; Cell Signaling Technology). Staining intensity was assessed by scoring on a 4-point scale (0, absent; 1, weak; 2, moderate; 3, strong). The subcellular compartment(s) showing the strongest staining (nucleus, cytoplasm, cell membrane) was recorded for each section and for the absence/presence of tumor tissue and any significant artifacts, as applicable. The assays were performed at the Applied Molecular Profiling Laboratory (University Health Network, Toronto, Canada) following standard operating procedures.

Results

Patients

Between July 2008 and October 2011, 37 patients were accrued at 3 sites in Canada (Table 1). All patients received at least 1 dose of study therapy and are included in the safety analysis. Thirty-one patients were evaluable for the primary end point: 1 patient was ineligible (determined on pathology review to have cervical cancer, not NSCLC), 3 withdrew consent without progression or toxicity that would mandate discontinuation after 6 doses, 1 and 2 cycles of therapy, respectively, and 2 were removed from study for adverse events in cycle 1.

Adverse Events and Treatment Delivery

Reported nonhematologic and hematologic adverse events considered by the investigator to be at least possibly related to protocol therapy are summarized in Tables 2 and 3, respectively. One patient died suddenly during cycle 2 of unknown causes. The most commonly reported nonhematologic adverse events were fatigue, gastrointestinal (diarrhea, nausea/vomiting, anorexia) and dermatologic. These were generally of only mild to moderate severity and easily managed. Two patients were discontinued from protocol therapy due to adverse events, both in cycle 1: 1 patient with a grade-3 lower gastrointestinal hemorrhage leading to grade-4 anemia and 1 patient with grade-3 pneumonitis with resulting grade-3 dyspnea and hypoxia. This latter resolved with antibiotics, diuretics, and withdrawal of saracatinib.

Hematologic toxicity was generally mild and of no clinical consequence except for the patient mentioned above. Biochemical

Table 2 Nonhematologic Adverse Events at Least Possibly Related and Occurring in at Least 2 Patients and/or of at Least Grade 3 in Severity

Adverse Event	No. of Patients With NCI CTCAE (v 3.0) Grade				
	0	1	2	3	4
Constitutional					
Chills	34	3	0	0	0
Fatigue	21	6	7	3	0
Fever	35	2	0	0	0
Weight Loss	35	2	0	0	0
Dermatologic					
Alopecia	34	3	0	0	0
Pruritis	35	2	0	0	0
Rash	30	7	0	0	0
Gastrointestinal					
Anorexia	21	10	6	0	0
Constipation	35	2	0	0	0
Diarrhea	23	11	0	3	0
Nausea	19	12	6	0	0
Vomiting	29	4	3	1	0
Hemorrhage					
Epistaxis	35	2	0	0	0
Gastroinstestinal	36	0	0	1	0
Neurological					
Dizziness	35	2	0	0	0
Pain					
Headache	33	4	0	0	0
Pulmonary					
Dyspnea	34	1	1	1	0
Hypoxia	36	0	0	1	0
Pneumonitis	36	0	0	1	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.

toxicity also was mild, with 1 episode each of grade-3 hypophosphatemia and elevation of alanine aminotransferase. Proteinuria was observed in 8 patients (one grade 3).

The 37 patients received a total of 131 cycles of therapy, with a median of 2 cycles per patient (range, 1−22). The planned dose intensity was 1225 mg/wk. The actual median dose intensity was 1204 mg/wk (range, 480−1225 mg/wk). Seven patients required an interruption of saracatinib, and 3 patients required a dose reduction (one each for grade-3 diarrhea, grade-3 proteinuria, and persistent grade-2 fatigue).

Table 3 Hematologic Toxicity

	N = 37				
	Worst CTC Grade, n				
	0	1	2	3	4
Leukocytes	29	6	2	0	0
Granulocytes	31	3	2	1	0
Lymphocytes	31	2	3	1	0
Hemoglobin	26	8	1	1	1
Platelets	29	5	3	0	0

Abbreviation: CTC = common terminology criteria.

Efficacy

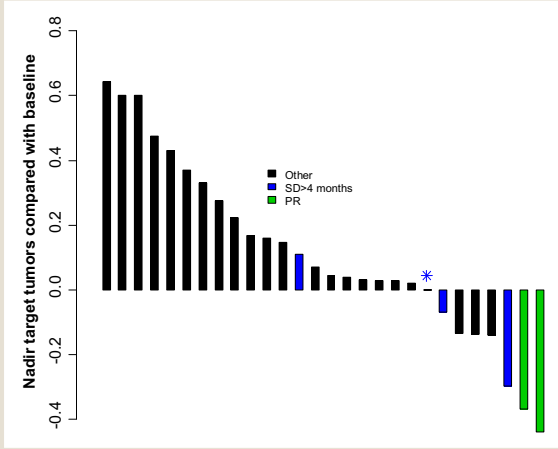
There were 2 partial responses, confirmed on independent review, lasting 3.7 months (adenocarcinoma) and 14.6 months (squamous carcinoma) (response rate in all 36 eligible patients, 5.5%, 95% confidence interval [CI] 2%−13%). An additional 4 patients, all with adenocarcinoma, had stabilization of disease for at least 4 cycles, leading to a disease control rate of 17% (95% CI, 4%−29%; Fig. 1); 2 of these 4 patients showed some reduction in their target lesions. According to the protocol, the patient who died suddenly in cycle 2 was considered to have disease progression. Therefore, there were 6 of 31 response-evaluable patients who met the primary end point of freedom from progression at cycle 4; an additional evaluable patient was not enrolled, as the criteria for declaring the therapy active could not be met.

Median progression-free survival was 1.8 months (95% CI, 1.6−2.8 months). Median survival of all eligible enrolled patients was 7.6 months (95% CI, 5.2−17.1 months) and the 1-year overall survival rate was 43% (95% CI, 26%−59%; Fig. 2).

Correlative Studies

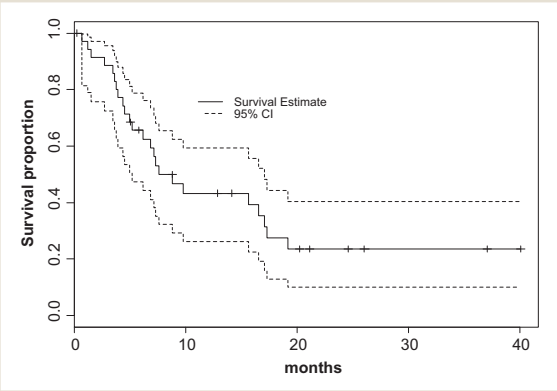
Adequate archival tissue was available for 23 patients, including 3 of those with prolonged stable disease, and 1 responding patient. Staining for phospho-src was not interpretable because of heterogeneity within samples, which was suggestive of artifact arising from delayed tissue fixation. Staining for src was cytoplasmic and/or membranous and 2+ to 3+ in all samples, and staining for csk was low to absent (0−1+) in all samples. As staining pattern was universal in all samples, no correlation with outcomes could be inferred for either src or csk.

Figure 1 Waterfall Plot of Responses. Note That 9 of 36 Eligible Patients had Only Baseline Measurements and are not Represented



Abbreviations: PR = partial responder; SD = stable disease.
*A patient with a 0% change.

Figure 2 Overall Survival, all Eligible Patients



The patient with the shorter response duration was found to have an *EGFR* exon 19 deletion (E746_A750del) confirmed by Sanger sequencing. The other responding patient was *EGFR* and *KRAS* wild type. No additional tissue was available for mutation analysis for any patient, including those patients with stable disease for at least 16 weeks.

Discussion

In this phase II trial in patients with platinum-pretreated advanced NSCLC, saracatinib demonstrated unexpected objective responses. In keeping with the phase I experience, fatigue and gastrointestinal complaints were the most common adverse events. These were, for the most part, easily managed, only rarely of grade-3 severity, and only infrequently required a dose interruption or reduction. One episode of pneumonitis possibly related to saracatinib was observed. Patients with advanced NSCLC have many possible potential causative factors for pneumonitis, including prior radiation, cytotoxic therapies, concomitant medications, infections, and progression of malignancy. However, pneumonitis has been observed in other trials of saracatinib,[8,11,12] and thus, this may be a rare but significant toxicity of this agent. The mechanism of the pneumonitis is unclear but may relate to its EGFR-inhibiting properties, as this is a known adverse effect of those agents. This inhibition may also be responsible for the mild acneiform and/or maculopapular rash observed in a few patients. In contrast to dasatinib, another inhibitor of src kinases that can lead to dyspnea due to the development of pleural effusions, no such events were observed in this trial.

Two independently confirmed partial responses were observed, 1 which lasted more than 14 months. Another 4 patients had stabilization of disease for at least 16 weeks; 1 of these patients had tumor reduction of 29% from baseline. Using IHC staining on archival tissue, no relationship between src or csk with outcomes was observed, and, given the ubiquitous expression of src in malignancy, this is not surprising. The IHC staining for p-src was considered uninterpretable, which is likely because of the lack of standardization in handling of archival tissue biopsy specimens at the time of initial processing that can lead to variability in the stability of protein phosphorylation status. Pretreatment levels of activated src expression did not correlate with outcomes in a trial of single-agent dasatinib in patients with advanced NSCLC.[13] Others have shown a high degree of correlation between p-src and src levels in cell lines.[7] Together, this suggests that p-src staining would not likely be useful as a predictive marker for treatment with src inhibitors.

This single-agent activity in advanced NSCLC is of interest, because objective responses to saracatinib were not observed in the phase I study nor in phase II trials in breast[11] head and neck[14] gastric[12] pancreatic,[15] or prostate[16] cancers, and given the initial hypothesis that src inhibitors would not likely result in tumor shrinkage. In a phase II trial of dasatinib in previously-untreated NSCLC, 1 partial response was observed in 34 patients.[13] Therefore, there may be a subpopulation of patients with NSCLC that benefit from src inhibition. It is known that src interacts with the EGFR pathway.[4] Inhibition of src leads to significant apoptosis in lung cancer cell lines harboring activating mutations of *EGFR* while rarely doing so in cell lines with wild-type *EGFR*.[17] One of the responding patients in the current trial had an activating *EGFR* mutation; whether this response was due to src or EGFR inhibition is unclear. In a trial of the combination of dasatinib with erlotinib,[18] 2 partial responses were observed: 1 patient had the identical exon 19 deletion in *EGFR* as the patient in the current trial, whereas the other, who had a squamous cell carcinoma, was *EGFR* wild-type. In the trial of single-agent dasatinib,[13] *EGFR* mutational status did not correlate with progression-free survival, and the 4 patients with prolonged stable disease and the 1 partial responder were all *EGFR* and *KRAS* wild type; additionally, several patients with *EGFR* mutations were enrolled to the trial who did not respond. Interestingly, a novel inactivating *BRAF* mutation was detected in the tumor of the responding patient.[19] Lung cancer cell lines transfected with such inactivating mutations were sensitive to the induction of apoptosis by dasatinib, and 1 cell line underwent senescence when exposed; this latter finding is in keeping with the clinical course in the patient who responded to dasatinib.

These data suggest that while *EGFR* mutational status may contribute to sensitivity to src inhibition, it alone is not sufficient to predict response to these agents. Some lung cancers with wild-type *EGFR* may still have some dependency on this pathway, as evidenced by the modest clinical benefit of erlotinib over best supportive care observed in a clinical trial of a mostly Western population with few *EGFR* mutations.[20] Therefore, combinations of src inhibitors with *EGFR* inhibitors may be beneficial in both *EGFR* mutant and wild-type NSCLC. The combination of dasatinib with erlotinib led to a disease control rate of 63% in a pretreated population of patients with advanced NSCLC.[18] A second trial of dasatinib with erlotinib in advanced NSCLC has been presented recently in abstract form.[21] In this trial, the only objective responses were observed in those with activating *EGFR* mutations; however, significant rates of disease stabilization were observed in those who were *EGFR* wild-type (12 of 26 patients).

Mutations in *DDR2* have been described recently in lung cancer and were detected in approximately 4% of patients with squamous cell carcinoma.[22] One such mutation was described in the patient with squamous cell carcinoma who responded to the combination of dasatinib and erlotinib. Inadequate tissue was available to determine if the responding patient with squamous cell carcinoma in the current

trial harbored a *DDR2* mutation. Although saracatinib has minimal activity against *DDR2*,[22] src kinases have been shown to be required for maximal *DDR2* kinase activity, and findings from preclinical studies demonstrated a marked reduction in proliferation of *DDR2* mutant cell lines on exposure to saracatinib.[22] Therefore, it is possible that saracatinib may have activity against *DDR2* mutant squamous cell NSCLC. Saracatinib has no activity against the fibroblast growth factor receptor tyrosine kinase, another potential target in a proportion of squamous cell carcinomas.[8]

Conclusion

Although this clinical trial did not meet its prespecified end point for declaring saracatinib an active agent in the second-line setting in NSCLC, it did show some evidence of single-agent activity, warranting further study. Unfortunately, mutational analyses were hampered by limited availability of samples. In particular, there was insufficient material to analyze from the patient who had a 29% reduction in tumor measurements and was undergoing saracatinib therapy for more than 1 year or to perform *DDR2* or *BRAF* mutational analysis on any patient. The design of future trials of src inhibitors as a single agent in lung cancer could consider limiting enrollment to those with *EGFR*, *DDR2*, and or inactivating *BRAF* mutations to determine if these are predictive markers for activity of these agents. Combination trials of src inhibitors with EGFR inhibitors could be considered in both *EGFR* mutated and wild-type patients. Additionally, there may be other, as yet unidentified, markers for benefit to src inhibitors, and this class of agents should continue to be investigated in NSCLC in biomarker discovery trials.

Acknowledgments

Supported by contracts HHSN261201100032C/NO1-CM-2011-00032.

Disclosure

V. Hirsh reports receiving honoraria from AstraZeneca for advisory boards. F. Shepherd reports receiving consultancy fees from AstraZeneca. G. Goss reports receiving consultancy fees and research funding from AstraZeneca. All other authors report no conflicts of interest relevant to this manuscript.

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