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A phase II trial of the Src-kinase inhibitor saracatinib after four cycles of chemotherapy for patients with extensive stage small cell lung cancer: NCCTG trial N-0621

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ABSTRACT

Introduction: To assess the efficacy and the Src-kinase inhibitor saracatinib (AZD-0530) after four cycles of platinum-based chemotherapy for extensive stage small cell lung cancer (SCLC).
Methods: Patients with at least stable disease received saracatinib at a dose of 175 mg/day by mouth until disease progression, unacceptable toxicity, or patient refusal. The primary endpoint was the 12-week progression-free survival (PFS) rate from initiation of saracatinib treatment. Planned interim analysis in first 20 patients, where 13 or more patients alive and progression-free at 12-weeks would allow continued enrollment to 40 total patients.
Results: All 23 evaluable patients received platinum based standard chemotherapy. Median age was 58 years (range: 48–82). 96% of patients had a performance status of 0/1. Median of two cycles given (range: 1–34). All 23 (100%) patients have ended treatment, most for disease progression (19/23). The 12-week PFS rate was 26% (6/23; 95% CI: 10–48%). From start of standard chemotherapy, median PFS was 4.7 months (95% CI: 4.5–5.1) and median OS was 11.2 months (95% CI: 9.9–13.8). Eight (35%) and three (13%) patients experienced at least one grade 3/4 or grade 4 AE, respectively. Commonly occurring grade 3/4 adverse events were thrombocytopenia (13%), fatigue (9%), nausea (9%), and vomiting (9%).
Conclusions: Saracatinib at a dose of 175 mg/day by mouth is well tolerated. However, the PFS rate observed at the pre-planned interim analysis did not meet the criteria for additional enrollment.

1. Introduction

This year approximately 28,500 Americans will be diagnosed with small cell lung cancer (SCLC) [1]. Of these, more than 60% will present with extensive-stage disease and nearly all will die from relapsed SCLC [2,3]. Chemotherapy with platinum (cisplatin or carboplatin) and etoposide has resulted in response rates of around 60–80%, median survival of 9–10 months and a 1-year survival rate of 35–40%. Several different approaches have been pursued to improve the outcomes of patients with SCLC. However, advances observed with systemic treatment of other solid tumors have not translated into any gains for patients with SCLC [4–7]. The addition of targeted therapy to standard treatments has also failed to improve outcomes in this condition [8].

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Src is a non-receptor tyrosine kinases closely associated with growth factor and cytokine receptors that plays a key role in cell adhesion, angiogenesis, invasion and motility of cancer cells [9]. Following activation by growth factor receptors, C-Src promotes survival via phosphorylation of the p85 subunit of phosphatidylinositide 3 kinase (PI3K) that results in activation of the AKT pathway. In addition, there is activation of the Ras/mitogen-activated protein kinase pathway through the transcription-3 (STAT3), STAT5, and Src [10–12]. The major consequence of increased Src activity is to promote an invasive tumor phenotype characterized by breakdown of cell–cell adhesion, increased cell–matrix adhesion, and formation of focal adhesions [12]. Accordingly, inhibition of Src activity in preclinical models restores cell–cell adhesion, inhibits cell migration and invasion, and reverses the Src-modulated invasive phenotype [13]. In addition, Src is frequently over expressed in lung cancer including SCLC and Src expression correlated with poor differentiation [13–15]. In SCLC, neuropeptide hormones like bombesin/gastrin-releasing peptide, galanin or bradykinin, seem to work as the main inducers of cell proliferation. Src kinase activities are crucial for neuropeptide-mediated GTP-loading of Ras and activation of extracellular signal-regulated kinases in SCLC cells [13]. Saracatinib is a potent Src inhibitor that modulates multiple key signaling pathways in cancer. In keeping with its mechanism of action, saracatinib has little effect on tumor growth in preclinical models, but does inhibit cancer cell invasion and metastasis in vitro and in vivo [16].

The present study was conducted by the North Central Treatment Group (NCCTG) to determine the 12-week progression free survival rate of patients with extensive stage SCLC treated with the oral Src-family kinase inhibitor saracatinib after four cycles of platinum-based chemotherapy.

2. Materials and methods

2.1. Overview

This phase II study was developed and conducted within the North Central Cancer Treatment Group (NCCTG). Institutional Review Boards of each NCCTG affiliated sites approved the study protocol. All patients were required to provide written consent prior to enrollment.

2.2. Eligibility criteria

Patients with a histologic or cytologic diagnosis of extensive-stage small cell lung cancer (SCLC) were potentially eligible for enrollment. Prior to receiving saracatinib treatment, patients received four cycles of a standard platinum-based chemotherapy regimen given every 3 or 4 weeks for a total of four cycles. Only those patients that did not progress on this initial standard chemotherapy were potentially eligible for enrollment. Patients were required to be at least 18 years of age, to have an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, and to have a life expectancy of at least 12 weeks. Hematologic and chemistry parameters were to be in the following ranges: white blood cell count $\geq 3.0 \times 10^9$/L, absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $\geq 100 \times 10^9$/L, hemoglobin >9.0 g/dL, total bilirubin <1.5 times the institutional upper normal limit (UNL), alkaline phosphatase $\leq$ 3 times the UNL, ALT and AST $\leq$3 times the UNL or AST and ALT $\leq$5 times the UNL if liver involvement, creatinine $\leq$1.5 times the UNL or creatinine clearance $\geq$60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

Contraindications included symptomatic, untreated, or uncontrolled CNS metastases or seizure disorder, although patients with CNS metastases treated with whole brain radiation therapy (WBRT) could be enrolled after completion of WBRT. In addition, patients with any clinically significant infection or any history of prior malignancy diagnosed within 5 years were not allowed study entry, with the exception of non-melanomatous skin cancer or cervical carcinoma in situ. Prior radiation therapy was only allowed if given with palliative intent. Other contraindications included use of St. John's Wort, history of allergic reactions to compounds of similar chemical or biologic composition to saracatinib. Patients were not eligible if pregnant or lactating and were required to use adequate contraception methods to prevent pregnancy during treatment. Finally, any patients receiving treatment known to be strong inhibitors of CYP3A4 were also not eligible.

2.3. Treatment

Saracatinib was provided by the National Cancer Institute. Patients first received four cycles of a platinum-based regimen. The choice of treatment between a cisplatin-based regimen and a carboplatin-based regimen was left up to the treating oncologist according to their best practice. Following this initial course of standard chemotherapy, patients that did not progress received an oral daily dose of 175 mg of saracatinib. The cycle length for saracatinib treatment was 3 weeks.

Patients that experienced a grade 4 hematologic or grade 3/4 non-hematologic adverse event that lasted greater than 5 days and did not resolve to a grade 2 or less, despite maximal supportive care, were to have their saracatinib dose reduced by one dose level to 125 mg. Any further dose reductions could not be lower than 100 mg of saracatinib and if adverse events did not resolve to grade 2 or less using this lowest dose level, the patients were to be followed in the event monitoring phase of the study. In addition, due to animal data suggesting that there may be a risk of adrenal gland damage with saracatinib, patients with symptoms consistent with adrenal insufficiency (i.e., low blood pressure, skin changes, depression, worsening fatigue, weight loss and weakness), underwent testing for adrenal gland function. If a patient experienced grade 2 or worse symptomatic adrenal insufficiency, saracatinib was to be discontinued and the patient was to be followed in the event monitoring phase of the study.

2.4. Evaluation, disease assessment, and follow-up

Prior to each cycle of treatment, patients underwent standard clinical and laboratory evaluation. Tumor assessments (chest X-ray, MRI, or CT) were performed every two cycles during treatment or anytime when disease progression was clinically suspected. Treatment with saracatinib was to continue every day until disease progression, unacceptable toxicity, patient refusal, investigator's decision to remove patient, or alternative treatment. Disease status was evaluated using Response Evaluation Criteria in Solid Tumors (RECIST) [17].

2.5. Statistical considerations

The primary endpoint for this trial was the 12-week PFS rate, calculated as the number of evaluable patients alive and progression-free at least 12 weeks post-registration, divided by the total number of evaluable patients. The primary analyses focuses on patients that received saracatinib treatment after having four cycles of platinum-based chemotherapy without disease progression. A two-stage design, with an interim analysis in the first 20 patients, was used to test whether there was sufficient evidence to determine that the 12-week PFS rate was at least 75% (i.e., clinically promising) versus at most 55% (i.e., clinically inactive). This study had 85% power to detect a 12-week PFS rate of 75%, with a .06 level of significance.

The decision rules for the design were as follows. If 13 or more of the first 20 evaluable patients were alive and progression-free for at least 12 weeks from study entry, the study would continue to a full accrual of 40 evaluable patients. If at least 27 of these 40 evaluable patients were alive and progression-free for at least 12 weeks from study entry, this would be considered adequate evidence of promising activity, and would warrant further testing of this regimen in subsequent studies. Otherwise, if 12 or fewer of the first 20 evaluable patients or 26 or fewer of the first 40 evaluable patients were alive and progression-free for at least 12 weeks, respectively, we would conclude that this treatment does not warrant further study in this patient population.

Secondary endpoints included adverse events, the confirmed response rate, PFS and overall survival (OS). Kaplan–Meier methodology [18] was used to describe the distribution of PFS and OS and SAS 9.1.3 was used for statistical analysis.

3. Results

3.1. Baseline characteristics

Between February, 2008 and August, 2008, 24 patients were enrolled through the NCCTG across 13 memberships. One patient was a cancelation prior to receiving saracatinib treatment and was removed from all analyses. The baseline characteristics for the 23 eligible patients are outlined in Table 1. The median age was 58 (range: 48–82), 9 (39%) of the patients were male, 22 (96%) had a PS of 0 or 1, most patients had a partial response (78%) to the standard platinum-based chemotherapy, and most patients had <10% weight loss (96%) within 3 months of study entry. Thirteen of the 23 patients (57%) received cisplatin-based standard chemotherapy, while the remaining patients received carboplatin-based chemotherapy.

Table 1
Patient baseline characteristics.

	Number
Age	
Mean (SD)	61.3 (10.07)
Median	58.0
Range	48–82
Gender	
Female	14 (60.9%)
Male	9 (39.1%)
Standard chemotherapy received	
Cisplatin based	13 (56.5%)
Carboplatin based	10 (43.5%)
Response to standard chemotherapy	
Stable disease (SD)	2 (8.7%)
Partial response (PR)	18 (78.3%)
Complete response (CR)	3 (13%)
Performance score	
0	8 (34.8%)
1	14 (60.9%)
2	1 (4.3%)
Weight loss within 3 months of study entry	
<5%	15 (65.2%)
5–10%	7 (30.4%)
>10%	1 (4.3%)

3.2. Outcome measures

All 23 patients were evaluable for the outcome measures of OS, PFS, and confirmed response (Table 2). The median follow-up was 23.6 months (range: 22.0–25.1) in the 2 patients still alive. Twenty-two (96%) patients have progressed and 21 (91%) have died. Six out of 23 (26%) patients were progression-free and alive at 12 weeks (95% CI: 10–48%), which did not meet our predefined criteria for continuation of the study to full accrual. Additionally, 2 out of 23 (9%) patients were progression-free and alive at 6 months (95% CI: 1–28%). The median PFS was 1.5 months (Fig. 1; 95% CI: 1.3–1.6), and the median OS was 7.8 months (Fig. 2; 95% CI: 6.9–10.6) from the start of saracatinib treatment. From the start of the standard chemotherapy regimen, the median PFS was 4.7 months (95% CI: 4.5–5.1), and the median survival was 11.2 months (95% CI: 9.9–13.8). Four patients had a best response of stable disease (SD) during saracatinib treatment and the other 19 patients had a best response of progression. No patients had a partial or complete response (Table 2).

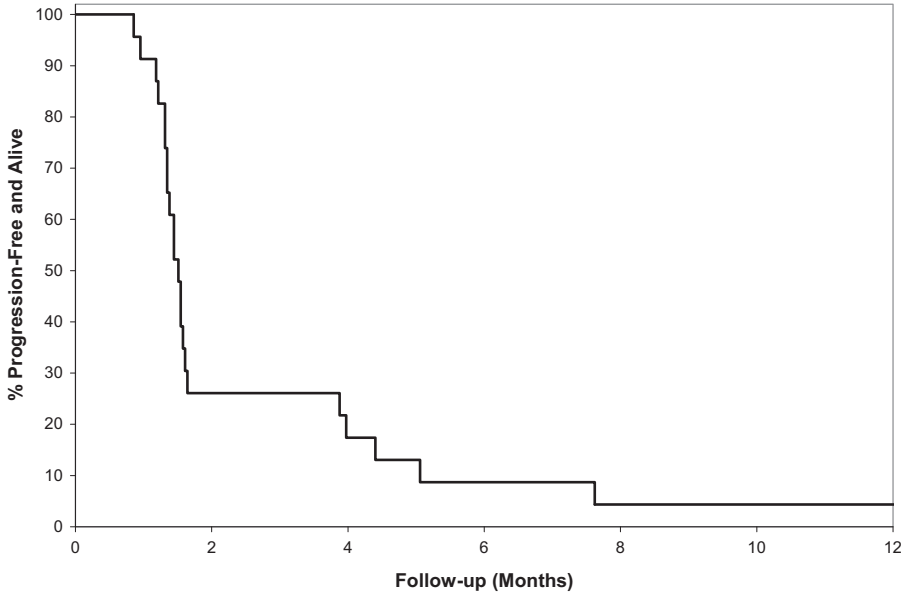

Fig. 1.

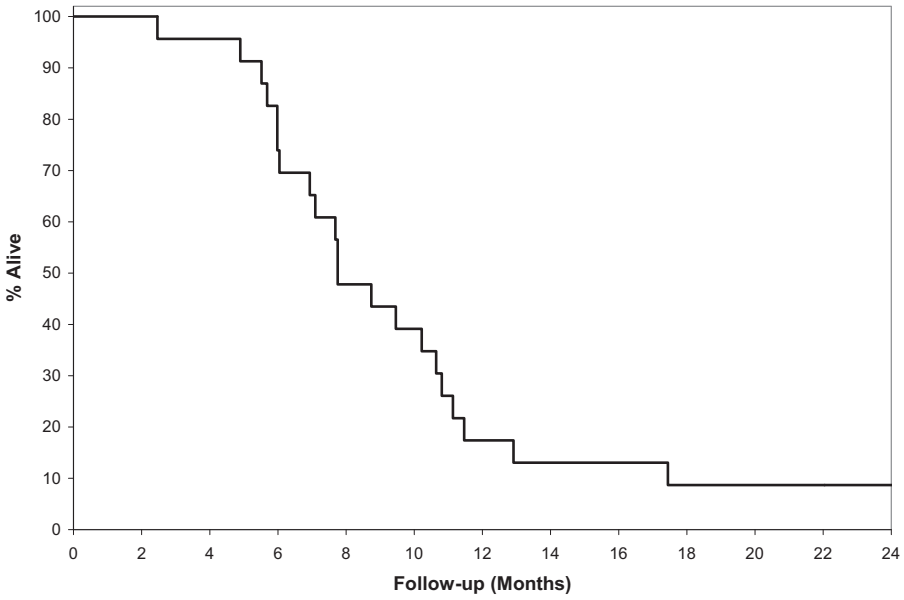

Fig. 2.

Table 2
Response, PFS, and OS efficacy outcomes.

Clinical outcome	*N* = 23
Best clinical response[a]	
Stable	4 (17%)
Progression	19 (83%)
12 week PFS	
Frequency, percentage (95% CI)[b]	6, 26% (10–48%)
Progression free survival (PFS)	
6-month % (95% CI)[b]	9% (1–28%)
Median months (95% CI)	1.5 (1.3–1.6)
Number progression-free (%)	1 (4.4%)
Survival (OS)	
6-month % (95% CI)	74% (58–94%)
Median months (95% CI)	7.8 (6.9–10.6)
Number alive (%)	2 (8.7%)

[a] Of the stable patients, two were complete responders (CR) at the start of AZD-0530.
[b] Exact binomial test confidence interval.

3.3. Treatment summary

A median of two cycles of saracatinib treatment were given (range: 1–34). No patients are still receiving saracatinib treatment. Of the 23 patients that discontinued saracatinib treatment, 19 (83%) discontinued early due to disease progression, 3 (14%) discontinued early due to adverse events, and one completed the study per protocol. For the first six cycles of treatment, most patients received the full dose of saracatinib. Specifically, 74% (17/23), 71% (15/21), 67% (4/6), 75% (3/4), 100% (3/3), and 100% (3/3) of the treated patients received full dose saracatinib for cycles 1–6, respectively (Table 3).

3.4. Adverse events

All 23 patients were evaluable for adverse events. Maximum severity grade 3/4 adverse events across all cycles of treatment (regardless of attribution to the saracatinib treatment) were reported (Table 4). Eight patients (35%) experienced at least one grade 3 or 4 AE and 3 patients (13%) experienced at least one grade 4 AE. One patient experienced a grade 4 thrombocytopenia (probably related to treatment), another patient experienced a grade 4 hypokalemia (probably related to treatment), and finally one patient experienced a grade 4 ARDS (probably related to treatment) and a grade 4 pneumonia with grade 0–2 ANC (possibly related to treatment). Commonly occurring grade 3/4 AEs were thrombocytopenia (13%), fatigue (9%), nausea (9%), and vomiting (9%). In addition, no patients had a grade 5 AE.

4. Discussion

SCLC accounts for 13% of all lung cancer cases diagnosed in the US [2]. The majority of SCLC patients present with extensive disease and are typically treated with a platinum-based agent and

Table 3
Saracatinib treatment information for first six cycles.

Saracatinib treatment information	1 (*N* = 23)	2 (*N* = 21)	3 (*N* = 6)	4 (*N* = 4)	5 (*N* = 3)	6 (*N* = 3)
Full dose received?[a]						
Yes	17 (73.9%)	15 (71.4%)	4 (66.7%)	3 (75%)	3 (100%)	3 (100%)
No	6 (26.1%)	6 (28.6%)	2 (33.3%)	1 (25%)	0 (0%)	0 (0%)
Percent of expected dose						
Mean (SD)	93.6 (14.5)	85.6 (31.8)	80.2 (36.4)	95.2 (9.5)	100.0 (0.0)	100.0 (0.0)
Median	100.0	100.0	100.0	100.0	100.0	100.0
Range	42.9–100.0	4.8–104.8	9.5–100.0	81.0–100.0	100.0–100.0	100.0–100.0

[a] A patient is considered to have received the full dose if the patient received ≥98% of the expected per protocol dose of the treatment (175 mg).

Table 4
Maximum severity (grade 3/4) adverse events across all cycles of treatment (regardless of attribution to the saracatinib treatment).

NCI CTC category[a]	Frequency (%) (*N* = 23 evaluable)	
	Grade 3	Grade 4
Hematologic		
Neutropenia	1 (4%)	0 (0%)
Leukopenia	1 (4%)	0 (0%)
Thrombocytopenia	2 (9%)	1 (4%)
Anemia	1 (4%)	0 (0%)
GI		
Nausea	2 (9%)	0 (0%)
Vomiting	2 (9%)	0 (0%)
Anorexia	1 (4%)	0 (0%)
Constipation	1 (4%)	0 (0%)
Miscellaneous		
Lower GI hemmorrhage	1 (4%)	0 (0%)
SGPT (ALT)	1 (4%)	0 (0%)
Bilirubin	1 (4%)	0 (0%)
Pneumonia with grade 0–2 ANC	0 (0%)	1 (4%)
Hyperglycemia	1 (4%)	0 (0%)
Hypokalemia	0 (0%)	1 (4%)
ARDS	0 (0%)	1 (4%)
Fatigue	2 (9%)	0 (0%)

[a] NCI CTCAE Version 3.0.

etoposide [3]. The combination of cisplatin and etoposide was initially introduced in 1985 and its superiority over non-platinum based regimes has been validated in two meta-analyses [6,19]. Subsequent phase III studies demonstrated that carboplatin with etoposide were less toxic and as effective as cisplatin etoposide as first line treatment of extensive stage SCLC [20,21].

Src family members have been implicated in the regulation of multiple oncogenic processes, but the weight of preclinical evidence suggests that their predominant role may be in the regulation of cancer cell invasion [22]. In addition, Src signaling plays a critical role in anchorage-dependent and -independent cell growth. These events occur through Src-mediated activation of the signal transducer and activator of transcription (STAT)-3 and focal adhesion kinase (FAK), both of which are also involved in tumor survival [23,24]. In addition, Src activates the VEGF pathway via STAT-3 and in response to hypoxia in human lung cancer cells, thus increasing the blood supply to the oxygen-starved tumor [25].

We designed this trial to obtain an initial cytoreduction of the tumor with four cycles of a platinum-based chemotherapy followed by a phase of consolidation treatment with saracatinib for patients with non-progressive disease. This trial was terminated early at the interim analysis because it did not meet the criteria needed to continue to full accrual, where only 6 out of 23 (26%) patients were progression-free and alive at 12 weeks (95% CI: 10–48%). No patients responded to saracatinib treatment, and only four patients had a best response of stable disease. The median PFS was 1.5 months and the median survival was 7.8 months from the start of saracatinib treatment. In this trial, saracatinib toxicities were mostly hematologic with some electrolyte abnormalities (hypokalemia) and infection.

These disappointing results add to several other negative trials using targeted therapies in patients with SCLC. These trials include imatinib [26–28], gefitinib [29], temsirolimus [30], oblimersen (bcl-2 anti-sense oligonucleotide) [31], tipifarnib (farnesyltransferase inhibitor) [32], marimastat (matrix metalloproteinase inhibitor) [33], exisulind (cGMP inhibitor) [34], bortezomib [35] and recently the Dasatinib [36]. Furthermore, the addition of bevacizumab, an agent active in NSCLC, to chemotherapy in phase II trials has not produced significant benefits for patients with SCLC [37,38]. At the present time, the combination of platinum and etoposide, a regimen used for almost three decades, continues to be the optimal therapy for patients with SCLC.

Conflict of interest statement

No conflict of interest.

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