Overview

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Title: A Phase I/II Study Combining Erlotinib and Dasatinib for Non-Small Cell Lung Cancer

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Disclosures

Ignacio I. Wistuba: Pfizer, Bayer, Eli Lilly, Genentech/Roche, GlaxoSmithKline, GeneCentric (C/A); Pfizer, Boehringer Ingelheim (H); Genentech, Bayer, Merck, Oncoplex, Myriad (RF); **George R. Blumenschein:** Bristol-Myers Squibb (C/A, RF); **Faye M. Johnson:** Bristol-Myers Squibb, Novartis (C/A). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Author Summary: Abstract and Brief Discussion

Background

EGFR and Src are frequently activated in non-small cell lung cancer (NSCLC). In preclinical models, combining EGFR and Src inhibition has additive synergistic effects. We conducted a phase I/II trial of the combination of Src inhibitor dasatinib with EGFR inhibitor erlotinib to determine the maximum tolerated dose (MTD), pharmacokinetic drug interactions, biomarkers, and efficacy in NSCLC.

Methods

The phase I 3+3 dose-escalation study enrolled patients with solid tumors to determine the MTD. The phase II trial enrolled patients with advanced NSCLC who had undergone no previous treatments to determine progression-free survival (PFS) and response. Pharmacokinetic and tissue biomarker analyses were performed.

Results

MTD was 150 mg of erlotinib and 70 mg of dasatinib daily based on 12 patients treated in the phase I portion. No responses were observed in phase I. The 35 NSCLC patients treated in phase II had an overall disease control rate of 59% at 6 weeks. Five patients (15%) had partial responses; all had activating *EGFR* mutations. Median PFS was 3.3 months. Epithelial-mesenchymal transition markers did not correlate with outcomes.

Conclusion

The combination of erlotinib and dasatinib is safe and feasible in NSCLC. The results of this study do not support use of this combination in molecularly unselected NSCLC.

Discussion

One strategy to enhance the efficacy of EGFR inhibitors in NSCLC is to combine them with Src inhibitors. This combination has additive effects in NSCLC cell lines in vitro, with synergistic effects observed in *EGFR* mutant cells [1–4]. In addition, NSCLC with an epithelial phenotype may be more sensitive to EGFR inhibition, and the addition of Src inhibition may overcome EGFR inhibitor resistance in mesenchymal tumors [5–10]. These findings led to the initiation of this study combining erlotinib with the Src inhibitor dasatinib [11–13] in NSCLC patients to evaluate the clinical activity of this combination and to test predictive biomarkers and pharmacokinetic interactions.

We performed a phase I/II study of this combination. The phase I portion enrolled patients with advanced solid tumors with any number of previous therapies. The phase II portion included stage IV NSCLC. The primary objective of the phase I portion was to assess the safety and tolerability of the combination and to determine the appropriate dose for phase II. The primary objective of the phase II portion was to determine the antitumor activity of the combination in NSCLC patients. Tumor size was assessed by computed tomography at baseline and every 6 weeks. We used existing tissue to assess E-cadherin and vimentin expression by immunohistochemistry [14] and to detect mutations in *EGFR* and *KRAS* by polymerase chain reaction, as described previously [14–16]. Erlotinib and dasatinib are both metabolized primarily by CYP3A4 [17–19]. Treatment with a CYP3A4 inhibitor or inducer increases or decreases exposure to both drugs, respectively [17, 18]. Dasatinib and erlotinib plasma concentrations were estimated, as described previously [20–22].

Based on 12 patients in phase I and in a similar study [23], we chose 150 mg of erlotinib and 70 mg of dasatinib daily for the phase II study. Toxic effects were consistent with those observed in previous studies with these agents. Five (15%) of 33 evaluable patients enrolled in the phase II study had partial responses, and no patients had complete responses. Fifteen patients (44%) had stable disease (Fig. 1). All responders had activating *EGFR* mutations; *EGFR* mutation status was associated with overall response rate (62% in mutant *EGFR* and 0% in wild-type *EGFR*, $p = .005$). Our pharmacokinetic results corroborate previous studies showing erlotinib-mediated inhibition of dasatinib clearance [24]. E-cadherin and vimentin expression did not correlate with efficacy. Our results do not support continued study of the combination of erlotinib and dasatinib in molecularly unselected NSCLC.

Trial Information

Disease	Lung cancer – NSCLC
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	One prior regimen
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	Progression-Free Survival
Secondary Endpoint	Overall Response Rate
Secondary Endpoint	Overall Survival
Secondary Endpoint	Correlative Endpoint
Additional Details of Endpoints or Study Design	The primary objective of the phase I portion of the study was to assess the safety and tolerability of the combination of dasatinib and erlotinib in patients with solid tumors to determine the appropriate dose for phase II. The primary objective of the phase II portion was to determine the antitumor activity of the combination of dasatinib and erlotinib in patients with NSCLC on the basis of the progression-free survival (PFS), The secondary objectives of phase II were to determine the response rate and overall survival (OS); to investigate the associations between clinical response and *EGFR* mutational status, *KRAS* mutational status, and expressions of E-cadherin, and vimentin in pretreatment tumor biopsies; and to determine the pharmacokinetic parameters for dasatinib and erlotinib.
Investigator's Analysis	Active but results overtaken by other developments

Drug Information

Drug 1	
Generic/Working name	Dasatinib
Trade name	Sprycel
Company name	Bristol-Myers Squibb
Drug type	Small molecule
Drug class	SRC
Dose	70 mg (mg) per flat dose
Route	Oral (po)
Schedule of Administration	Daily
Drug 2	
Generic/Working name	Erlotinib
Trade name	Tarceva
Company name	Astellas
Drug type	Small molecule
Drug class	EGFR
Dose	150 mg (mg) per flat dose
Route	Oral (po)
Schedule of Administration	Daily

Patient Characteristics

Number of patients, male	26
Number of patients, female	21
Stage	IV
Age	Median (range): 62
Number of prior systemic therapies	Median (range): 0 (0-4)
Performance Status:	ECOG 0 — 10 1 — 37 2 — 0 3 — 0 unknown — 0
Cancer Types or Histologic Subtypes	NSCLC (Squamous) 11 NSCLC (Adenocarcinoma) 25 NSCLC 5 Mesothelioma 2 SCLC 1 HNSCC 2 Adenoid Cystic Carcinoma 1

Primary Assessment Method

Experimental Arm: Total Patient Population

Number of patients screened	53
Number of patients enrolled	47
Number of patients evaluable for toxicity	46
Number of patients evaluated for efficacy	33
Evaluation method	Other
Response assessment CR	0%
Response assessment PR	5%

Response assessment SD	15%
Response assessment PD	13%
Response assessment other	2%
(Median) duration assessments PFS	3.3 months, CI: 2.04
(Median) duration assessments TTP	months
(Median) duration assessments OS	13 months, CI: 6.41
(Median) duration assessments response duration	140 days
(Median) duration assessments duration of treatment	49 days

Adverse Events

Name	NC/NA	1	2	3	4	5	All Grades
Diarrhea	36%	54%	8%	0%	0%	0%	63%
Rash: acne/acneiform	43%	30%	23%	2%	0%	0%	56%
Dyspnea (shortness of breath)	58%	2%	21%	17%	0%	0%	41%
Pruritus/itching	93%	4%	2%	0%	0%	0%	6%
ALT, SGPT (serum glutamic pyruvic transaminase)	89%	10%	0%	0%	0%	0%	10%
Hair loss/alopecia (scalp or body)	95%	4%	0%	0%	0%	0%	4%
Anorexia	76%	15%	8%	0%	0%	0%	23%
AST, SGOT(serum glutamic oxaloacetic transaminase)	78%	19%	2%	0%	0%	0%	21%
Bilirubin (hyperbilirubinemia)	91%	4%	4%	0%	0%	0%	8%
Creatinine	89%	8%	2%	0%	0%	0%	10%
Fatigue (asthenia, lethargy, malaise)	45%	15%	28%	10%	0%	0%	54%
Edema: limb	91%	8%	0%	0%	0%	0%	8%
Hemoglobin	50%	28%	21%	0%	0%	0%	50%
Hemorrhage, pulmonary/upper respiratory	97%	2%	0%	0%	0%	0%	2%
Calcium, serum-low (hypocalcemia)	80%	15%	4%	0%	0%	0%	19%
Sodium, serum-low (hyponatremia)	84%	8%	0%	4%	2%	0%	15%
Phosphate, serum-low (hypophosphatemia)	78%	8%	0%	13%	0%	0%	21%
Hypoxia	91%	0%	4%	2%	0%	2%	8%
Pleural effusion (nonmalignant)	69%	10%	13%	6%	0%	0%	30%
Infection with normal ANC or Grade 1 or 2 neutrophils	91%	0%	4%	4%	0%	0%	8%
Mucositis/stomatitis (clinical exam)	89%	6%	2%	2%	0%	0%	10%
Nausea	50%	39%	6%	4%	0%	0%	50%
Neutrophils/granulocytes (ANC/AGC)	97%	0%	0%	2%	0%	0%	2%
Pain	67%	19%	6%	6%	0%	0%	32%
Pericardial effusion (nonmalignant)	97%	0%	0%	2%	0%	0%	2%
Platelets	82%	13%	2%	2%	0%	0%	17%
Thrombosis/thrombus/embolism	93%	0%	4%	0%	2%	0%	6%
Vomiting	82%	13%	2%	2%	0%	0%	17%

These data represent all cycles' toxicities.
Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Name	Grade	Attribution
Myocardial infarction	5	Unrelated

Assessment, Analysis, and Discussion

Completion	Study completed
Pharmacokinetics / Pharmacodynamics	Correlative Endpoints Met
Investigator's Assessment	Active but results overtaken by other developments

Discussion

NSCLC continues to pose a formidable challenge in clinical practice. Erlotinib is most effective in *EGFR*-mutant NSCLC [25] but also has activity in wild-type *EGFR* disease [26]. EGFR and Src are both overexpressed in NSCLC, and this overexpression is associated with disease progression [27]. The combination of Src inhibitors and EGFR inhibitors has at least additive cytotoxic effects in NSCLC cell lines in vitro, with synergistic effects observed in cell lines with *EGFR* mutations [1, 2]. These encouraging preclinical findings led to the initiation the current study, which demonstrates that the combination of erlotinib and dasatinib is safe and feasible in advanced NSCLC. The maximum tolerated dose was 150 mg of erlotinib and 70 mg of dasatinib daily. The dose-limiting toxicities were hypophosphatemia, fatigue, and hyponatremia. The most commonly observed toxic effects were acne and diarrhea, which were usually low grade and could be managed effectively with supportive medications. Fatigue was also very common. As with other tyrosine kinase inhibitor combinations [28, 29], the dose of dasatinib was lower than the standard dose (100 mg/day to 70 mg b.i.d.) due to toxicity of the combination.

In this unselected patient population, the combination treatment was associated with a response rate of 15% and a disease control rate (partial response plus stable disease) of 59% at 6 weeks, similar to the response and control rates reported previously with this combination treatment [23]. All responses occurred in patients with *EGFR* mutations. The median progression-free survival (PFS) and overall survival (OS) times were 3.3 and 13 months, respectively; these survival durations are somewhat better than those reported in the literature for single-agent erlotinib in unselected groups of patients with NSCLC. In the BR.21 study, patients receiving second- or third-line erlotinib had a median PFS time of 2.2 months and a median OS time of 6.7 months [26]. In the TORCH trial, unselected patients with NSCLC who received front-line erlotinib had a median PFS time of 2.2 months and a median OS time of 8.7 months [30]. Our improved outcomes may be due to the small size of our study or to an additive effect of dasatinib. The observation that dasatinib did not reverse resistance to erlotinib, either alone or in combination with erlotinib, in *EGFR*–mutant NSCLC in a previous phase II study [31], and the absence of any responses in patients with wild-type *EGFR* in the current study supports the former conclusion that our favorable results may be related to small sample size and patient selection.

All 18 patients for whom pharmacokinetic analysis was conducted received the phase II doses. The pharmacokinetic parameters of erlotinib were calculated for the first dose (day -3) and at steady state (day 19), and parameters for dasatinib were calculated at steady state (day 19). Erlotinib's single-dose and steady-state parameters are similar to those seen in previous studies [23, 32–34]. As seen in previous studies [35], significant interpatient variability was observed for both erlotinib and dasatinib (Fig. 2). Erlotinib clearance was significantly lower at steady state than after single-dose administration (2.63 ± 1.30 and 5.7 ± 2.9 L/hour, $p = .0324$). Like Haura and colleagues [23], we found that concomitant administration of dasatinib did not alter erlotinib exposure in NSCLC patients. Interestingly, the steady-state dasatinib parameters seen in this study showed a longer half-life, lower clearance, and greater dose-adjusted exposure than those reported in previous studies [19, 36–38], supporting erlotinib-mediated inhibition of dasatinib clearance and potentially contributing to the need for dasatinib dose reduction [24] (Table 1).

Our study has several limitations. Our sample size was relatively small, with only 35 patients in the phase II portion. Many enrolled patients did not have sufficient tissue for biomarker analyses, limiting the power of these analyses. Still, although the biomarker studies showed no relationship between expression levels of E-cadherin or vimentin and patient outcomes, the epithelial-mesenchymal transition is a complex process that cannot be represented by only these two markers.

Our results do not support continued study of the combination of erlotinib and dasatinib in molecularly unselected NSCLC. Previous research has identified kinase-inactivating *BRAF* mutations and *DDR2* mutations as possible markers of dasatinib sensitivity in NSCLC [13, 39]. We did not test for these mutations because we saw no responses in *EGFR*-wild type patients. Erlotinib remains a standard and effective treatment for *EGFR*-mutant NSCLC or unselected NSCLC progressing on prior therapy [26, 40].

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Figures and Tables

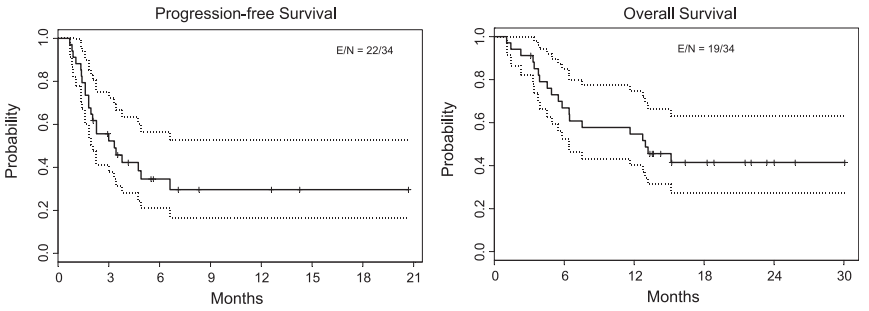

Figure 1. Kaplan Meier Curves showing progression-free and overall survival durations for 34 evaluable patients in the phase II study. Abbreviations: E, events (i.e., progression or death); N, total number of patients.

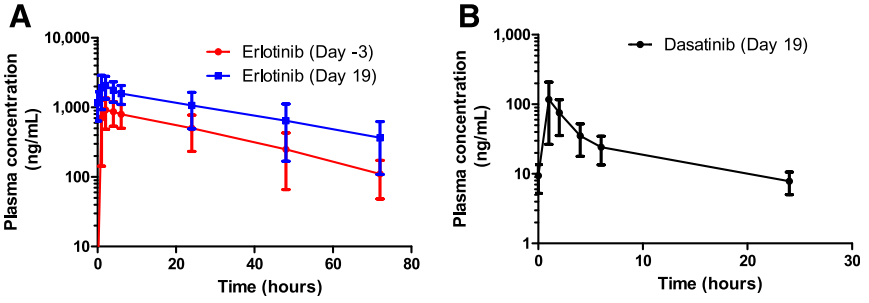

Figure 2. Mean (± SD) plasma concentrations of erlotinib and dasatinib over time.

Table 1. Pharmacokinetics of dasatinib and erlotinib

Parameter	Treatment day, cycle 1		
	Erlotinib day −3 ($n = 18$)	Erlotinib day +19 ($n = 11$)	Dasatinib day +19 ($n = 14$)
Dose-adjusted AUC (h × μg/L/mg)	235.8 ± 177.8	544.74 ± 289.9	8.6 ± 3.0
$AUC_{0-\infty}$ (h × μg/L)	35,369.1 ± 26,674.3	81,710.3 ± 43,490.6	602.1 ± 253.1
AUC_{0-24} (h × μg/L)	15,951.5 ± 6,134.2	33,977.5 ± 12,649.3	531.7 ± 234.8
Clearance (L/h)	5.7 ± 2.9	2.4 ± 1.3	143.1 ± 73.0
C_{max} (ng/mL)	1,803.4 ± 414.3	2,144.4 ± 761.6	123.5 ± 84.8
Terminal plasma half-life (h)	24.5 ± 14.6	27.7 ± 10.6	7.5 ± 4.2
Ke (L/h)	0.04 ± 0.02	0.03 ± 0.02	0.1 ± 0.1
T_{max} (h)	2.9 ± 1.4	2.1 ± 1	1.3 ± 0.5
V (L)	168.1 ± 70	80.1 ± 29	1,434.7 ± 847.4

Data are shown as mean ± SD. For patients participating in pharmacokinetic studies, a single dose of erlotinib was given 3 days before treatment with combination therapy. Blood samples for pharmacokinetic analysis were collected on the first day of erlotinib administration (day −3, cycle 1) and on day 19 (cycle 1) of erlotinib and dasatinib administration at 0, 1, 2, 4, 6, 8, 24, 48, and 72 hours after administration.

Abbreviations: AUC, area under the curve representing plasma concentration over time; $AUC_{0-\infty}$, area under the curve representing plasma concentration from 0 hours to infinity; AUC_{0-24}, area under the curve representing plasma concentration from 0 to 24 hours; C_{max}, maximum observed plasma concentration; h, hours; Ke, elimination constant; T_{max}, time to reach maximum plasma concentration; V, volume of distribution.

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