

Activity of Sunitinib in Patients With Advanced Neuroendocrine Tumors

Matthew H. Kulke, Heinz-Josef Lenz, Neal J. Meropol, James Posey, David P. Ryan, Joel Picus, Emily Bergsland, Keith Stuart, Lesley Tye, Xin Huang, Jim Z. Li, Charles M. Baum, and Charles S. Fuchs

From the Dana-Farber Cancer Institute; Massachusetts General Hospital; Beth Israel Deaconess Medical Center, Boston, MA; University of Southern California Norris Comprehensive Cancer Center, Los Angeles; University of California, San Francisco Comprehensive Cancer Center, San Francisco; Pfizer Global Research and Development, La Jolla, CA; Fox Chase Cancer Center, Philadelphia, PA; University of Alabama, Birmingham, AL; and Washington University, St Louis, MO.

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Sources of preliminary data are listed in the Appendix available online.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Matthew Kulke, MD, Dana-Farber Cancer Institute, 44 Binney St, Boston, MA 02115, e-mail: Matthew_Kulke@dfci.harvard.edu.

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A B S T R A C T

Purpose

Standard cytotoxic chemotherapy has limited efficacy in metastatic neuroendocrine tumor patients. Neuroendocrine tumors express vascular endothelial growth factor (VEGF) and its receptor (VEGFR). Sunitinib malate, an oral tyrosine kinase inhibitor, has activity against VEGFRs as well as platelet-derived growth factor receptors, stem-cell factor receptor, glial cell line–derived neurotrophic factor, and FMS-like tyrosine kinase-3. We evaluated the efficacy of sunitinib in a two-cohort, phase II study of advanced carcinoid and pancreatic neuroendocrine tumor patients.

Patients and Methods

Patients were treated with repeated 6-week cycles of oral sunitinib (50 mg/d for 4 weeks, followed by 2 weeks off treatment). Patients were observed for response, survival, and adverse events. Patient-reported outcomes were assessed.

Results

Among 109 enrolled patients, 107 received sunitinib (carcinoid, $n = 41$; pancreatic endocrine tumor, $n = 66$). Overall objective response rate (ORR) in pancreatic endocrine tumor patients was 16.7% (11 of 66 patients), and 68% (45 of 66 patients) had stable disease (SD). Among carcinoid patients, ORR was 2.4% (one of 41 patients), and 83% (34 of 41 patients) had SD. Median time to tumor progression was 7.7 months in pancreatic neuroendocrine tumor patients and 10.2 months in carcinoid patients. One-year survival rate was 81.1% in pancreatic neuroendocrine tumor patients and 83.4% in carcinoid patients. No significant differences from baseline in patient-reported quality of life or fatigue were observed during treatment.

Conclusion

Sunitinib has antitumor activity in pancreatic neuroendocrine tumors; its activity against carcinoid tumors could not be definitively determined in this nonrandomized study. Randomized trials of sunitinib in patients with neuroendocrine tumors are warranted.

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INTRODUCTION

Carcinoid and pancreatic neuroendocrine tumors are characterized by indolent behavior, characteristic well-differentiated histologic features, and the ability to secrete neuropeptides resulting in characteristic clinical syndromes.¹ The most common of these is the carcinoid syndrome, which is associated with high serotonin levels, episodic flushing, diarrhea, and right-sided valvular heart disease.^{2,3} When neuroendocrine tumors are diagnosed at an early stage, surgical resection is often curative.⁴ Unfortunately, curative surgery is rarely an option for patients with advanced disease.⁵

Palliative options for patients with advanced neuroendocrine tumors are limited. Approximately 90% of neuroendocrine tumors express somatostatin receptors.⁶ Although somatostatin analogs are

effective in ameliorating hormonal secretion symptoms, they only rarely result in tumor regression.^{7,8} Interferon alfa therapy has been associated with objective tumor responses in up to 10% of patients with advanced neuroendocrine tumors, but may be associated with fatigue, myelosuppression, and depression.⁹ Approximately one third of patients with pancreatic neuroendocrine tumors experience objective responses after therapy with streptozocin- or temozolomide-based combination chemotherapy regimens.¹⁰⁻¹³ These regimens are less effective in patients with advanced carcinoid tumors; moreover, their prolonged use is often associated with toxicity.¹⁴

The highly vascular nature of neuroendocrine tumors led to initial interest in angiogenesis inhibition as a treatment modality in this disease.¹⁵ Overexpression of vascular endothelial growth factor

(VEGF), together with VEGF receptor (VEGFR) subtypes, has been observed in both carcinoid and pancreatic endocrine tumors, suggesting that autocrine activation of the VEGF pathway may promote tumor growth.¹⁶⁻¹⁸ Inhibition of VEGFR with function-blocking antibodies disrupted tumor growth in a mouse pancreatic neuroendocrine tumor model, providing further support for this hypothesis.¹⁹ A number of other signaling pathways have also been implicated in neuroendocrine tumors, which also express platelet-derived growth factor (PDGF), PDGF receptor (PDGFR), insulin-like growth factor-1, insulin-like growth factor receptor, basic fibroblast growth factor, transforming growth factor α and β , epidermal growth factor receptor, and stem-cell factor receptor.²⁰⁻²⁸

Sunitinib malate (SUTENT; Pfizer Inc, New York, NY) is a small-molecule kinase inhibitor with activity against a number of tyrosine kinase receptors, including VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α , PDGFR- β , stem-cell factor receptor, glial cell line-derived neurotrophic factor receptor (rearranged during transfection), and FMS-like tyrosine kinase-3 (Pfizer Inc, data on file).²⁹⁻³² In a phase I trial of sunitinib, antitumor activity was reported in patients with renal cell carcinoma (RCC) and GI stromal tumors (GIST) and in one of four patients with neuroendocrine tumors.³³ Subsequent trials in both RCC and GIST confirmed antitumor activity and safety in these tumor types,³⁴⁻³⁷ leading to approval by the US Food and Drug Administration and the European Medi-

cines Agency for use in advanced RCC patients who are treatment naïve or who experience relapse after interleukin-2 or interferon alfa treatment and in GIST patients after disease progression on or intolerance to imatinib therapy.

We performed a phase II, open-label, multicenter study to assess the safety and efficacy of sunitinib in patients with advanced neuroendocrine tumors. Eligible patients with carcinoid and pancreatic endocrine tumors received repeated 6-week treatment cycles of sunitinib administered at an oral dose of 50 mg once daily for 4 weeks, followed by 2 weeks off treatment. In light of the tumor regression observed in the phase I study, radiologic response was chosen as the primary end point of the present study. Patients were also observed for time to response/progression, survival, and toxicity. Patient-reported outcomes and drug exposure levels were assessed.

PATIENTS AND METHODS

Patients

Patients were enrolled at eight centers in the United States between March 2003 and November 2005. All patients had histologic evidence of carcinoid or pancreatic endocrine tumor and were not candidates for curative surgery. Patients with small-cell carcinoma were excluded. All patients had measurable disease per the Response Evaluation Criteria in Solid Tumors (RECIST)³⁸; an Eastern Cooperative Oncology Group performance status of

Table 1. Baseline Characteristics of the Study Population

Characteristic	Diagnosis Cohort			
	Carcinoid Tumor (n = 41)		Pancreatic Tumor (n = 66)	
	No. of Patients	%	No. of Patients	%
Sex				
Male	22	53.7	42	63.6
Female	19	46.3	24	36.4
Age, years				
Median	58		56	
Range	34-73		32-81	
ECOG performance status				
0	21	51.2	36	54.5
1	20	48.8	30	45.5
Time since initial diagnosis, range in months	0.8-272.5		0.4-149.4	
Primary diagnosis				
Carcinoid	40	97.6		
Foregut: lungs, stomach	14	34.1		
Midgut: small bowel, appendix	19	46.3		
Hindgut: colon, rectum	7	17.1		
Pancreatic neuroendocrine tumor			65	98.5
Functioning			19	28.8
Gastrinoma			5	7.6
Insulinoma			3	4.5
VIPoma			2	3.0
Glucagonoma			4	6.1
Other			5	7.6
Nonfunctioning			46	69.7
Unknown	1	2.4	1	1.5
Receiving octreotide at baseline	22	53.7	18	27.3
Previous surgery	40	97.6	65	98.5
Previous radiotherapy	6	14.6	11	16.7
Previous systemic therapy	18	43.9	40	60.6

Abbreviations: ECOG, Eastern Cooperative Oncology Group; VIPoma, vasoactive intestinal peptide secreting tumor.

0 or 1; adequate hepatic, hematologic, and renal function; and either an echocardiogram or multiple-gated acquisition scan that demonstrated preserved left ventricular ejection fraction. Treatment with prior chemotherapy, embolization, or radiotherapy was permitted. Patients receiving stable doses of somatostatin analogs were allowed to continue receiving these treatments. Patients who had prior treatment with VEGF pathway inhibitors, known brain metastases, a history of cardiac arrhythmias, or evidence of myocardial ischemia or cerebrovascular accident within 12 months were excluded. All patients signed informed consent, and the study was approved by the institutional review boards of the participating institutions. The trial was registered (www.clinicaltrials.gov/ct/gui/show/NCT00056693) and performed in accordance with International Conference on Harmonization Good Clinical Practice

guidelines, the Declaration of Helsinki (1996), and applicable local regulatory requirements and laws.

Study Treatment

Patients self-administered sunitinib at a starting dose of 50 mg by mouth daily for 4 weeks followed by 2 weeks off treatment in repeated 6-week cycles. In patients without significant toxicity, dose escalation to 62.5 mg and 75 mg was permitted (but not required) at the discretion of the investigator and after discussion with the study sponsor. Patients with significant grade 3 or 4 toxicities underwent dose reduction to 37.5 mg and 25 mg. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Concomitant treatment with drugs having dysrhythmic potential

Table 2. Adverse Events in Patients With Carcinoid and Pancreatic Tumors (N = 107) Based on National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0)

Adverse Event	Grade 1		Grade 2		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Treatment-related, nonhematologic adverse events*								
Fatigue	33	30.8	36	33.6	26	24.3	0	0
Diarrhea	47	43.9	18	16.8	5	4.7	0	0
Nausea	36	33.6	15	14.0	6	5.6	0	0
Dysgeusia	45	42.1	7	6.5	0	0	0	0
Skin discoloration	28	26.2	11	10.3	0	0	0	0
Glossodynia	21	19.6	12	11.2	3	2.8	0	0
Myalgia	17	15.9	16	15.0	2	1.9	0	0
Stomatitis	14	13.1	18	16.8	2	1.9	0	0
Hair color changes	28	26.2	6	5.6	0	0	0	0
Vomiting	18	16.8	7	6.5	7	6.5	0	0
Anorexia	20	18.7	7	6.5	3	2.8	0	0
Rash	21	19.6	6	5.6	1	0.9	0	0
Oral pain	17	15.9	9	8.4	0	0	0	0
Headache	16	15.0	8	7.5	1	0.9	0	0
Flushing	20	18.7	1	0.9	0	0	0	0
Dyspepsia	16	15.0	4	3.7	0	0	0	0
Paresthesia	16	15.0	3	2.8	0	0	0	0
Hand-foot syndrome	14	13.1	2	1.9	2	1.9	0	0
Hypertension	3	2.8	3	2.8	11	10.3	0	0
Periorbital edema	17	15.9	0	0	0	0	0	0
Dehydration	5	4.7	6	5.6	5	4.7	0	0
Pain in extremity	12	11.2	2	1.9	1	0.9	0	0
Arthralgia	10	9.3	4	3.7	1	0.9	0	0
Dizziness	14	13.1	1	0.9	0	0	0	0
Mucosal inflammation	6	5.6	2	1.9	3	2.8	0	0
Insomnia	7	6.5	4	3.7	0	0	0	0
Pulmonary embolism†	0	0	0	0	0	0	1	0.9
GI hemorrhage‡	0	0	0	0	0	0	2	1.9
Lipase increased	0	0	0	0	0	0	1	0.9
Cardiac failure congestive	0	0	0	0	0	0	1	0.9
Cerebrovascular accident	0	0	0	0	0	0	1	0.9
Hyponatremia	0	0	0	0	2	1.9	1	0.9
Treatment-emergent, hematologic adverse events								
Anemia	61	57.0	23	21.5	3	2.8	0	0
Leukopenia§	41	38.3	42	39.3	15	14.0	0	0
Lymphopenia	4	3.7	55	51.4	28	26.2	0	0
Neutropenia	20	18.7	34	31.8	31	29.0	5	4.7
Thrombocytopenia¶	39	36.4	25	23.4	9	8.4	0	0

NOTE. One grade 5 treatment-related adverse event occurred and was a result of GI hemorrhage.

*Incidence cutoff \geq 10% of patients.

†No patient experienced deep vein thrombosis or vena cava thrombosis.

‡Includes GI hemorrhage and lower GI hemorrhage.

§Data missing for three patients at baseline.

||Data missing for four patients at baseline.

¶Data missing for seven patients at baseline.

(terfenadine, quinidine, procainamide, disopyramide, sotalol, propracol, bepridil, haloperidol, risperidone, and indapamide) was not allowed.

Study Evaluations

Biochemical and hematologic parameters were assessed at baseline and every 2 weeks during the first cycle; thereafter, hematologic parameters were measured every 2 weeks, and biochemical parameters were measured on the first and last treatment days of each cycle. Multiple-gated acquisition or echocardiogram measurement of left ventricular ejection fraction was performed at screening and at the end of odd-numbered cycles.

Computed tomography or magnetic resonance imaging was performed at screening, at the end of cycle 1 and each odd-numbered cycle, if disease progression was suspected, and at study end or patient withdrawal, if a scan had not been performed within the previous 6 weeks. All responses were confirmed at least 4 to 6 weeks after initial documentation of response. Objective tumor response was assessed using RECIST.³⁸ Patients were observed after treatment discontinuation for survival status.

Blood samples for determination of predose (day 1) and trough (day > 1) concentrations of sunitinib and its active metabolite (SU12662) were collected on treatment days 1, 14, and 28 of cycles 1, 2, and 3, respectively; on day 1 of cycles ≥ 4 ; and at end of treatment.

General health-related quality of life was assessed using the EuroQol Group's EQ-5D self-report questionnaire,³⁹ and self-reported fatigue was assessed using the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale.⁴⁰ Patients completed the EQ-5D assessment on days 1 and 28 of treatment cycles 1 to 6 and at end of treatment/withdrawal visit. Patients completed the FACIT-Fatigue assessment at baseline (cycle 1, day 1), weekly through cycle 4, and at the end of treatment.

Statistical Methods

This study used an open-label, two-cohort, Simon two-stage design⁴¹ to test the null hypothesis that the true objective response rate (ORR) was $\leq 5\%$

versus the alternative hypothesis that the true response rate was $\geq 15\%$. Sixty-three patients were required in each cohort (carcinoid and pancreatic neuroendocrine tumor) to detect the response difference with 85% power and a significance level of 5%. In each cohort, 38 patients were treated in stage 1. If ≤ 1 objective tumor response was observed in the first 38 treated patients in either cohort, then enrollment in that cohort was to be terminated. However, if ≥ 2 objective tumor responses were observed in the first 38 treated patients, then the cohort was to be expanded to enroll 63 treated patients.

Secondary end points included time to objective tumor response (time from the first sunitinib dose to the first documentation of objective tumor response), time to tumor progression (TTP; time from the first sunitinib dose to the first documentation of objective tumor progression, initiation of other/additional anticancer therapy, or patient withdrawal as a result of unknown reasons), and overall survival (time from the first sunitinib dose to the date of death as a result of any cause). All time-to-event data (time to objective tumor response, TTP, and overall survival) were described using the Kaplan-Meier method.

RESULTS

Patient Characteristics and Treatment

Of the 109 enrolled patients, 107 (41 carcinoid patients and 66 pancreatic neuroendocrine tumor patients) were treated with sunitinib. Characteristics of treated patients are listed in Table 1. The median sunitinib doses administered in the carcinoid and pancreatic neuroendocrine cohorts were 50.0 mg (range, 28.0 to 53.9 mg) and 49.6 mg (range, 28.3 to 58.3 mg), respectively. Sixty-seven patients (62.6%) had at least one dosing interruption, 51 patients (47.7%) had

Table 3. Efficacy of Sunitinib by Diagnosis Cohort

Parameter	Carcinoid Tumor (n = 41)		Pancreatic Tumor (n = 66)	
	No. of Patients	%	No. of Patients	%
Best overall response				
Complete response	0	0.0	0	0.0
Partial response	1	2.4	11	16.7
Stable disease	34	82.9	45	68.2
≥ 6 months	23	56.1	37	56.1
Progressive disease	1	2.4	5	7.6
Not assessable	4	9.8	3	4.5
Missing	1	2.4	2	3.0
Overall objective response rate	1	2.4	11	16.7
95% CI, %*	0.1 to 12.9		8.6 to 27.9	
Time to tumor response, months				
No. of patients†	1		11	
Median‡	3.7		4.0	
Range			2.6-6.7	
95% CI for median	NA		3.7 to 6.5	
Time to tumor progression, months				
No. of patients	41		66	
Patients censored	23	56.1	34	51.5
Median‡	10.2		7.7	
Range	0.02-19.0§		0.02-15.3§	
95% CI for median	9.2 to 17.5		6.5 to 12.5	
1-year survival	41	83.4	66	81.1
95% CI, %	66.7 to 92.3		67.3 to 89.5	

Abbreviation: NA, not applicable.
 *Using exact method based on F distribution.
 †For time to tumor response, only patients with confirmed responses are included.
 ‡From the Kaplan-Meier estimate.
 §Indicates a censored observation.

a dose reduction, and three patients had dose increases to 62.5 mg daily. Of the 107 patients who began treatment, 94 (37 with carcinoid tumors and 57 with pancreatic tumors) received more than one treatment cycle, and 65 patients (24 with carcinoid tumors and 41 with pancreatic tumors) began \geq five cycles of treatment (approximately 6 months). The median time on treatment was 7.2 months (range, 0.9 to 19.4 months). The median follow-up duration was 13.4 months, with a median duration of 15.1 months for patients with carcinoid tumors and 12.5 months for patients with pancreatic tumors. The most common reasons for treatment discontinuation were disease progression ($n = 45$), completion of therapy ($n = 30$; all 30 patients completed six cycles of therapy and continued therapy on a continuation protocol), withdrawal of consent ($n = 20$), and adverse events (AEs; $n = 11$). Of the patients who withdrew consent, 11 withdrew consent before initiation of their fifth treatment cycle, and nine withdrew consent after initiation of cycle 5.

Pharmacokinetics

In patients with carcinoid tumors, median trough concentrations of sunitinib, SU12662, and total drug (sunitinib + SU12662) were 49, 21, and 71 ng/mL, respectively, on days 14, 21, and/or 28 of cycles 1 to 3; corresponding values for patients with pancreatic neuroendocrine tumors were 37, 20, and 60 ng/mL, respectively, on days 14, 21, and/or 28 of cycles 1 to 3. These values approximated the preclinically determined therapeutic total drug concentration of more than 50 ng/mL needed to inhibit receptor phosphorylation and cause tumor regression.²⁹ Median total drug concentrations on day 1 of cycle 2 and of all subsequent cycles were less than 3 ng/mL in both cohorts, suggesting nearly complete drug washout between cycles.

AEs

Fatigue was the most common treatment-related AE and developed in 95 patients (88.8%) overall (Table 2). In most patients, fatigue was mild; 26 patients experienced grade 3 fatigue, and none experienced grade 4 fatigue. Other common AEs included diarrhea, nausea, dysgeusia, glossodynia, and skin discoloration. Hypertension, a toxicity also observed with other VEGF pathway inhibitors, was observed in 15.9% of the patient population and was more common among carcinoid patients (19.7%) than among patients with pancreatic neuroendocrine tumors (9.8%). Grade 3 hypertension was reported in 10.3% of patients; no incidents of grade 4 hypertension were reported. Treatment-related grade 4 AEs were reported infrequently and included GI hemorrhage (1.9%), pulmonary embolism (0.9%), increased lipase (0.9%), cardiac congestive failure (0.9%), cerebrovascular accident (0.9%), and hyponatremia (0.9%; Table 2). A single treatment-related death was caused by GI hemorrhage. Grade 3 or 4 neutropenia and thrombocytopenia developed in 33.7% and 8.4% of patients, respectively (Table 2). A higher incidence of grade 3 leukopenia was observed in patients with pancreatic tumors versus carcinoid cancers (18.2% *v* 7.3%, respectively; no grade 4 leukopenia was reported).

Efficacy

The ORR in the pancreatic endocrine tumor cohort was 16.7% (Table 3). Responders included one patient with gastrinoma, one patient with a vasoactive intestinal peptide tumor, and nine patients with nonfunctioning pancreatic endocrine tumors. One patient with a foregut carcinoid tumor had a confirmed re-

sponse. The lack of at least two confirmed partial responses among carcinoid tumor patients in the first enrollment stage precluded further enrollment of carcinoid patients. Overall, 43.9% of carcinoid patients and 62.1% of the pancreatic neuroendocrine tumor patients seemed to demonstrate some degree of tumor shrinkage (Figs 1A and 1B). The majority of these patients had stable disease (SD) by RECIST. The overall rate of SD was 68.2% among pancreatic neuroendocrine tumor patients and 82.9% among carcinoid patients.

The median TTP was 10.2 months for patients with carcinoid tumors and 7.7 months for patients with pancreatic neuroendocrine tumors (Fig 2A). One-year survival rate was 83.4% in carcinoid patients and 81.1% in pancreatic neuroendocrine tumor patients (Table 3 and Fig 2B).

Patient-Reported Outcomes

Assessable EQ-5D questionnaires were received from 90% to 100% of available patients at each assessment on days 1 and 28 of treatment cycles 1 to 6. No significant changes in the EQ-5D index or EQ-5D visual analog scale scores were evident during the first six cycles of treatment (Figs 3A and 3B). Completion rates for FACIT-Fatigue questionnaires during the first four cycles of treatment were 84% to 99% on days 1, 7, 14, 21, and 28 and 47% to 78% on day 35. Although the mean FACIT-Fatigue score remained relatively stable for each treatment cycle, a pattern of modest increases in patient-reported fatigue during the dosing period with recovery during the off-treatment periods seemed evident (Fig 3C).

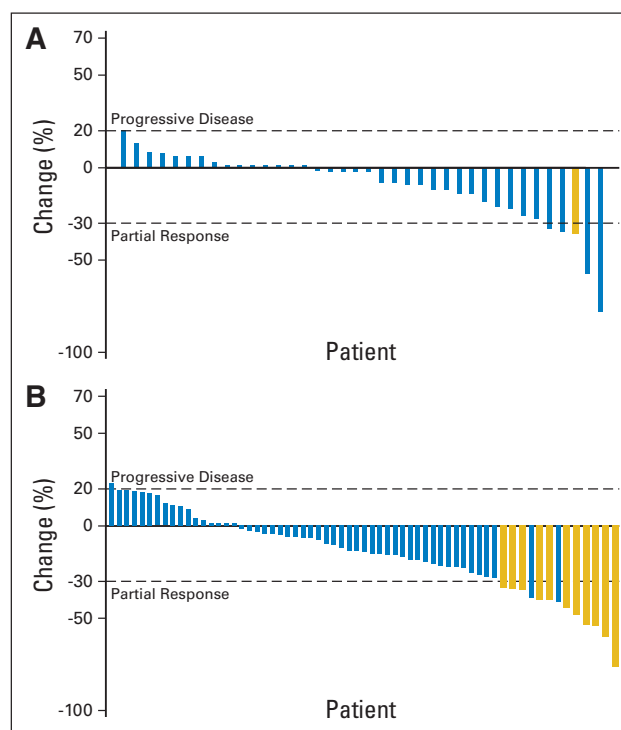


Fig 1. Investigator-assessed maximum percent reduction in tumor lesions in patients with (A) carcinoid and (B) pancreatic neuroendocrine tumors. Patients delineated in gold (wider bars) were classified as having partial responses by Response Evaluation Criteria in Solid Tumors.

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