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ORIGINAL REPORT

Activity of SU11248, a Multitargeted Inhibitor of Vascular Endothelial Growth Factor Receptor and Platelet-Derived Growth Factor Receptor, in Patients With Metastatic Renal Cell Carcinoma

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ABSTRACT

Purpose
Renal cell carcinoma (RCC) is characterized by loss of von Hippel Lindau tumor suppressor gene activity, resulting in high expression of pro-angiogenic growth factors: vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). SU11248 (sunitinib malate), a small molecule inhibitor with high binding affinity for VEGF and PDGF receptors, was tested for clinical activity in patients with metastatic RCC.

Patients and Methods
Patients with metastatic RCC and progression on first-line cytokine therapy were enrolled onto a multicenter phase II trial. SU11248 monotherapy was administered in repeated 6-week cycles of daily oral therapy for 4 weeks, followed by 2 weeks off. Overall response rate was the primary end point, and time to progression and safety were secondary end points.

Results
Twenty-five (40%) of 63 patients treated with SU11248 achieved partial responses; 17 additional patients (27%) demonstrated stable disease lasting ≥ 3 months. Median time to progression in the 63 patients was 8.7 months. Dosing was generally tolerated with manageable toxicities.

Conclusion
SU11248, a multitargeted receptor tyrosine kinase inhibitor of VEGF and PDGF receptors, demonstrates antitumor activity in metastatic RCC as second-line therapy, a setting where no effective systemic therapy is presently recognized. The genetics of RCC and these promising clinical results support the hypothesis that VEGF and PDGF receptor-mediated signaling is an effective therapeutic target in RCC.

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INTRODUCTION

Renal cell carcinoma (RCC) accounts for more than 30,000 new cases of cancer and more than 12,000 deaths in the United States annually.[1] Patients with RCC metastases have a poor prognosis, with few other solid tumor cell types showing such uniform resistance to cytotoxic chemotherapy agents.[2] Over decades of drug testing, only interleukin-2 (IL-2) has demonstrated enough clinical activity to warrant a US Food and Drug Administration indication for treatment of metastatic RCC.[1,2] In pivotal trials, high-dose intravenous IL-2 administered in an intensive care unit setting demonstrated a 14% partial or complete response rate.[3] Other cytokine regimens, including lower doses of subcutaneously administered interferon alfa (IFN-α), have demonstrated the same or lower response rates, but with better tolerance.[4,5] These two strategies represent the near sum of options available to patients with metastatic RCC, and no proven treatments exist for patients whose disease has progressed despite cytokine therapy. Overall median survival after progression after cytokine therapy is only 12 months, and the median survival is approximately 7 months in patients with an unfavorable clinical feature, such as anemia or decreased performance status.[6]

There are several recognized subtypes of RCC, but more than 80% of all tumors demonstrate clear-cell carcinoma histology. Cytogenetic studies have demonstrated frequent and early loss of heterozygosity in chromosome 3p 25-26 in 90% or more of

spontaneous clear cell carcinomas.[7,8] The high frequency of clear cell RCC in patients with von Hippel Lindau (VHL) syndrome led investigators to identify the *VHL* gene in this setting.[9] Subsequent sequencing analyses have demonstrated additional *VHL* mutations in the remaining allele in 50% to 60% of clear cell carcinomas.[10] Further second-hit silencing by hypermethylation and other epigenetic mechanisms likely account for even higher rates of biallelic gene loss.[11] Restoration of *VHL* function in *VHL* (−/−) RCC cell lines suppresses their ability to form tumors in nude mice xenograft models, supporting the hypothesis that *VHL* is a renal cancer tumor suppressor gene, which when inactivated leads to disease progression.[12]

Elucidation of VHL protein function in cells has identified targets for therapy in this highly resistant malignancy.[13] The VHL gene product normally forms stable complexes with elongin B, elongin C, cullin 2, and Rbx1 that regulate the protein degradation of hypoxia inducible factor-alpha (HIF-α).[14] When VHL protein function is absent, HIF-α is allowed to accumulate and bind with constitutively present HIF-β,[13] forming a transcriptional factor complex resulting in unregulated expression of hypoxia-inducible genes, including vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These growth factors are secreted and bind to specific tyrosine kinase receptors on the surface of endothelial cells and vascular pericytes, respectively, resulting in cell migration, proliferation, and survival. Phenotypically, these growth factors promote tumor angiogenesis that may contribute to the hypervascular histology of RCC.[1] Consequently, inhibition of VEGF and PDGF signaling pathways may reverse in part the physiologic consequences of losing VHL protein function and may inhibit tumor growth.

SU11248 (sunitinib malate) is a highly potent, selective inhibitor of certain protein tyrosine kinases, including VEGF-R types 1 to 3, PDGF-*R*-α, and PDGF-*R*-β.[15-19] Preclinical data suggest that SU11248 has antitumor activity that may result from both inhibition of angiogenesis and direct antiproliferative effects on certain tumor cell types.[15-19] A phase I clinical study of SU11248 demonstrated evidence of antitumor activity in several patients with metastatic RCC, supporting the working hypothesis that RCC represented an ideal proof-of-concept tumor type for further study of this dual VEGF and PDGF receptor inhibitor.[20] The recommended dose for phase II trials was defined in phase I trials as 50 mg orally once daily for 4 weeks, followed by 2 weeks off, in repeated 6-week cycles.[20,21] Using this schedule, a multicenter, phase II clinical trial was conducted to assess the clinical efficacy and safety of SU11248 in patients with cytokine-refractory metastatic RCC.

PATIENTS AND METHODS

Patients

Sixty-three patients were enrolled onto the study between January and July 2003. Eligibility criteria included informed consent, histologic confirmation of RCC, measurable disease with evidence of metastases, failure of one cytokine (IFN-α, IL-2) -based therapy because of disease progression or unacceptable toxicity, Eastern Cooperative Oncology Group performance status of 0 or 1, normal serum amylase and lipase, a normal adrenocorticotropic hormone stimulation test, and adequate hematologic, hepatic, renal, and cardiac function. The latter was determined as a normal left ventricular ejection fraction by echocardiogram or multigated acquisition (MUGA) scan. Patients were excluded for the presence of brain metastases or ongoing cardiac dysrhythmia, prolongation of QT_c interval, or any significant cardiac event within the previous 12 months.

The study was approved by the institutional review board at each of the seven participating centers and was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Study Design and Treatment

The starting dose of SU11248 was 50 mg per day administered in repeated 6-week cycles of daily therapy for 4 weeks, followed by 2 weeks off. SU11248 was self-administered orally once daily without regard to meals. Intrapatient dose escalation by 12.5 mg/d (up to 75 mg/d) was permitted in the absence of treatment-related toxicity. Dose reduction for toxicity was allowed to 37.5 mg/d and then to 25 mg/d, according to a nomogram for grade 3 to 4 severity.

Evaluation

Baseline evaluations included medical history and physical examination; computed tomography scan of the chest, abdomen, and pelvis; bone scan (in patients with known bone metastases); assessment of Eastern Cooperative Oncology Group performance status; CBC; biochemical profile (including serum amylase and lipase); cardiac function (12-lead ECG and either an echocardiogram or MUGA scan); and adrenocorticotropic hormone stimulation test. The rigorous evaluations of cardiac, adrenal, and pancreatic function were incorporated in the study as safety assessments based on preclinical data.

Assessment of Efficacy, Safety, and Quality of Life

Objective clinical response was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) using computed tomography or magnetic resonance imaging scan and bone scan (if bone metastases were present at baseline) after cycles 1, 2, and 4, and every two cycles thereafter until the end of treatment. CBC, cardiac enzymes, and biochemical profiles were obtained throughout the study. Cardiac function was assessed by ECG and echocardiogram or MUGA scan on day 28 of each treatment cycle. Quality of life was assessed using the Functional Assessment of Chronic Illness Therapy–Fatigue scale (FACIT-Fatigue) and the EuroQoL EQ-5D instrument (EQ-5D). Patients completed the FACIT-Fatigue questionnaire before receiving SU11248 on day 1 (as the baseline assessment) and weekly for cycles 1 through 4 and the EQ-5D on days 1 and 28 of each cycle.

SU11248 treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Individual patients continued SU11248 treatment after progression if the investigator felt that the patient continued to derive clinical benefit. However, for purposes of analysis, the patient was considered to have met the study end point of disease progression. Response was assessed by investigators according to RECIST criteria and severity of adverse events according to the National Cancer Institute Common Toxicity Criteria version 2.0.

Assessment of SU11248 Levels and Biomarkers

Plasma concentrations of SU11248 and its active metabolite, SU12662, were determined on days 1 and 28 of cycles 1 to 4. Plasma concentrations of SU11248 and SU12662 were determined predose by a liquid chromatography/mass spectrometry method at BASi (West Lafayette, IN), with a lower limit of detection of 0.1 ng/mL for SU11248 and SU12662.

Plasma samples were collected on days 1 and 28 of each cycle for assessment of soluble proteins that may be correlates of angiogenic activity and/or pharmacodynamic inhibition of VEGF receptor-mediated signaling.[20-22] Each cycle consisted of 4 weeks of treatment followed by 2 weeks off. Soluble proteins were analyzed with enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN). The VEGF-A ELISA assay measured the VEGF-A_{165} and VEGF-A_{121} isoforms. A soluble form of VEGF-R2 (sVEGF-R2) was quantified with an ELISA that measured the extracellular (soluble) domain of VEGF-R2.[23] An ELISA assay for placenta growth factor (PlGF) was also used (PlGF is a VEGF family member and a specific ligand of VEGF-R1).[24]

Statistical Evaluations

The primary end point was objective tumor response rate (complete response or partial response, as defined by RECIST). Sample size was determined using Simon's Minimax two-stage design.[25] Sixty-three treated patients were required for evaluation of the hypothesis that the objective tumor response rate was ≥ 15%, with an alpha level of 5% and 85% power. Time-to-event variables were estimated using the Kaplan-Meier method.[26]

RESULTS

Patient Characteristics

Sixty-three patients were treated with SU11248 (Table 1). The median age was 60 years, and 55 patients (87%) had clear cell histology. Only four patients (6%) had achieved a complete or partial response to the prior cytokine therapy.

Efficacy

All 63 patients received the study drug and were included in the analysis of efficacy end points. Partial responses determined by RECIST were achieved in 25 patients (40%; 95% CI, 28% to 53%; Table 1). Best response of stable disease for ≥ 3 months was observed in an additional 17 patients (27%). Twenty-one patients (33%) had either progressive or stable disease of less than 3 months duration or were not assessable.

Table 1. Patient Characteristics and Best Responses to SU11248 Treatment

Characteristic	No.	%
Total	63	100
Sex		
Male	43	68
Female	20	32
Age, years		
Median	60	—
Range	24-87	—
ECOG performance status		
0	34	54
1	29	46
Prior nephrectomy		
Yes	58	92
No	5	8
Prior systemic treatment		
Interferon-alpha*	35	56
IL-2*	19	30
Interferon-alpha + IL-2*	9	14
Radiation therapy	25	40
Histology		
Clear cell	55	87
Papillary	4	6
Sarcomatoid variant (not otherwise specified)	1	2
Unspecified	3	5
Site of metastatic disease		
Lung	52	81
Liver	10	16
Bone	32	51
No. of metastatic sites		
1	8	13
≥ 2	55	87
MSKCC risk factors for second-line therapy[6]		
0	34	54
≥ 1	29	46
Best response to SU11248 treatment		
Partial response	25	40
Stable disease for ≥ 3 months	17	27
Progressive disease, stable disease for < 3 months or not assessable	21	33

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IL-2, interleukin-2; MSKCC, Memorial Sloan-Kettering Cancer Center.
*May have included additional agents other than cytokines.

The majority of patients had a reduction in measurable disease. Figure 1 shows each patient's maximum percentage of tumor reduction at the time of analysis achieved during treatment with SU11248. Percentages were calculated using the summed unidimensional measurements of target lesions per RECIST.

Each of the patients with a partial response had evidence of progressive disease at the time of study entry. The median time to first observation of partial response was 2.3 months. Twenty-four partial responders had clear cell histology, and one had a papillary-cell type. Responding lesions included sites of local recurrence and lymphatic, hepatic, pulmonary, bone, and adrenal metastases, examples of which are shown in patients who achieved partial responses (Fig 2). These images highlight responses in multiple metastatic sites, as well as in the large primary tumor in patient 1 (Figs 2A, 2B, and 2C), multiple hepatic, lung, and pleural metastases in patient 2 (Figs 2D and 2E), and a large retroperitoneal lymphadenopathy and hepatic metastases in patient 3 (Figs 2F and 2G). Also noted in images of patient 3 (Fig 2F), there is decreased attenuation of the retroperitoneal masses consistent with tumor necrosis and response.

Tumor images suggested treatment with SU11248 resulted not only in regression in tumor size, but also in qualitative changes in contrast uptake that accompanied or preceded tumor regressions. This observation raises the possibility that changes in tumor perfusion may be a pharmacodynamic marker of SU11248 effect. Figure 3 demonstrates an example in which lack of contrast enhancement and marked central low attenuation within the hepatic masses after initial treatment led to an apparent increase in tumor size, reflecting interval response with tumor necrosis. Soft tissue and pulmonary lesions concomitantly regressed, and subsequent scans revealed regression of hepatic metastases and an overall partial response after three cycles.

Of 25 patients who achieved a partial response, 15 patients experienced disease progression, two patients discontinued treatment due to adverse events, and eight patients remain on therapy and are progression free at 21+ to 24+ months from the start of therapy at the time of analysis. Median time to progression for the 63 patients was

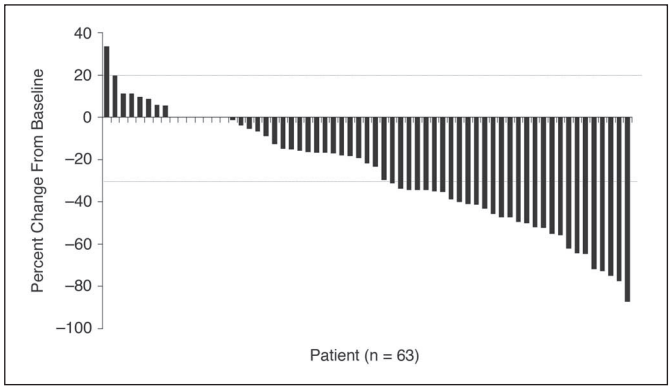

Fig 1. Maximal percentage of tumor reduction for target lesions by Response Evaluation Criteria in Solid Tumors (RECIST).

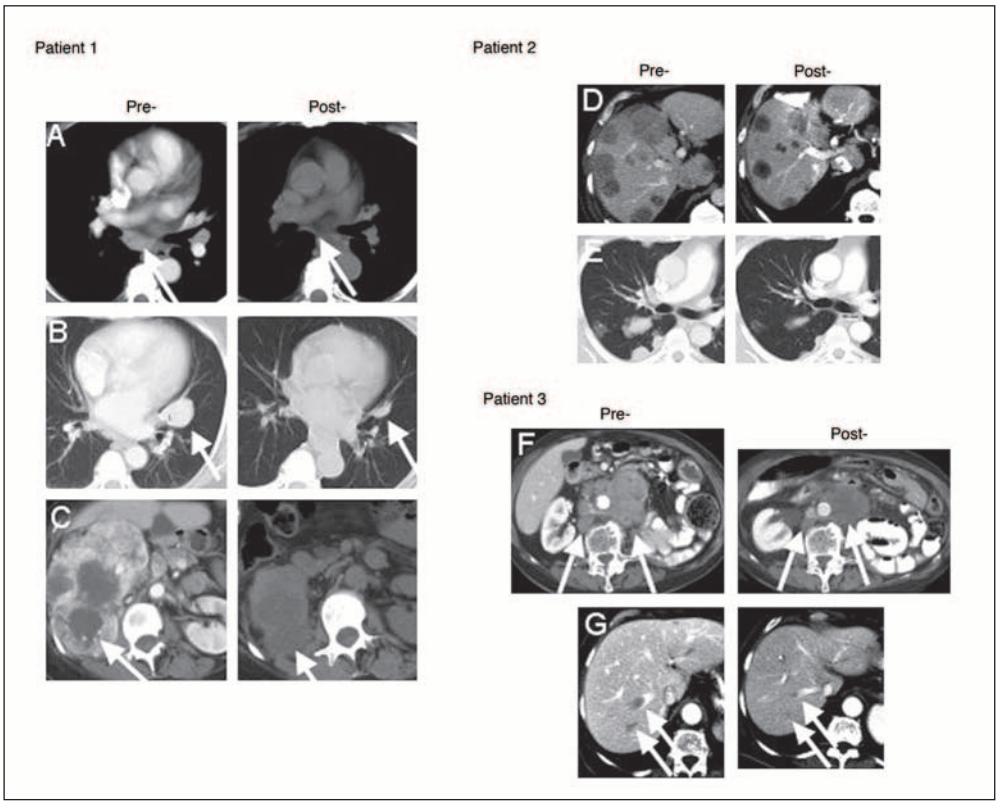

Fig 2. Computed tomography scan images of responding lesions from three patients who achieved partial responses: (A,B,C) responses in patient with multiple metastatic sites from a large primary renal tumor after treatment; (D,E) responses in patient 2 with multiple hepatic, lung, and pleural metastases; (F,G) responses in patient 3 with large retroperitoneal lymphadenopathy and hepatic metastases.

8.7 months (95% CI, 5.5 to 10.7; Fig 4A) and median survival was 16.4 months (95% CI, 10.8 to NA [not yet attained]; Fig 4B).

Treatment Administration and Adverse Events

Median duration of treatment was 9 months (range, < 1 to 24+ months). The most common adverse event was fatigue, which was categorized as grade 3 severity in seven patients (11%; Table 2). The most frequently occurring grade 3 to 4 laboratory abnormalities included lymphopenia without infection (32%) and elevated serum lipase (21%) without clinical signs or symptoms of pancreatitis. No patient developed adrenal insufficiency associated with SU11248 treatment. Four patients were removed from the study per protocol for a decline in cardiac ejection fraction; three patients were without clinical signs and symptoms, and the fourth patient was noted to have dyspnea.

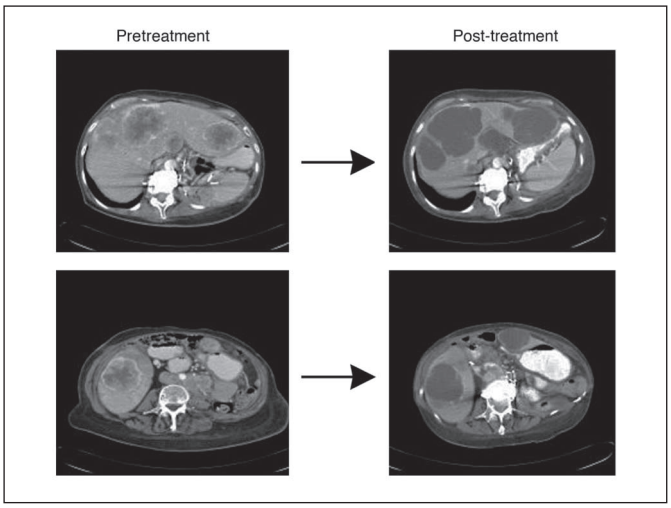

Fig 3. Tumor responses of hepatic metastases: Computed tomography scan images through the liver of a patient after one cycle of treatment with SU11248. Before treatment, several hepatic metastases are apparent. After the first cycle of treatment, the lesions demonstrate lack of enhancement and marked low attenuation consistent with tumor necrosis.

Dose reductions were performed in 22 patients (35%) from 50 to 37.5 mg/d, and the dose for two of these patients was further reduced to 25 mg/d. Common reasons for dose reductions included asymptomatic hyperlipasemia or hyperamylasemia (11 patients, per protocol) and fatigue (five patients). The dose was escalated in five patients from 50 to 62.5 mg/d and in one patient to 75 mg/d, with no evidence of improved response.

Quality of Life

Assessable baseline EQ-5D questionnaires were received from 60 patients. Questionnaires were consistently returned from ongoing patients, with compliance rates at or above 95% at each assessment on days 1 and 28 of cycles 1 through 4. Mean and median baseline health state visual analog scale scores (77.1 and 80.0, respectively, of a possible 100) indicated that the study population's quality of life before SU11248 treatment was similar to that of an age-matched US general population.[27] Mean and median health state visual analog scale scores were similar to the baseline scores through 24 weeks of treatment (data not shown).

Valid baseline questionnaires for the FACIT-Fatigue scale were received from 62 patients. Questionnaires were consistently returned from ongoing patients, with compliance rates at or greater than 90% for each weekly assessment from cycle 1 through

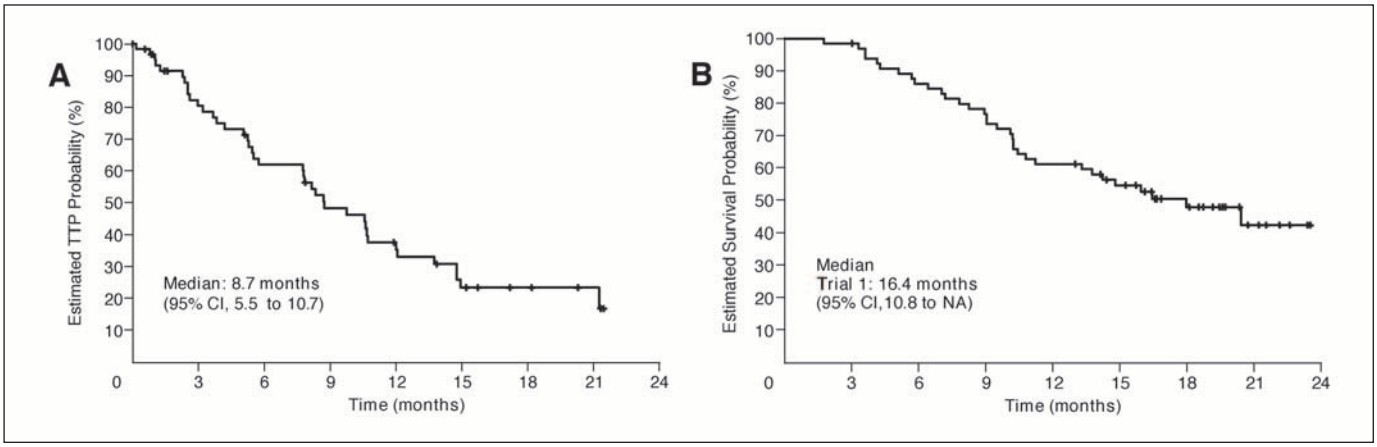

Fig 4. Kaplan-Meier plots of (A) time to tumor progression (TTP) and (B) overall survival. NA, not yet attained.

the end of cycle 4 dosing. Mean and median baseline scores for the study population were 40.4 and 44, respectively, which is similar to the scores (40.0 and 42, respectively) of a nonanemic cancer population but lower than the scores (43.6 and 47, respectively) of a general United States population.[28] Median and mean fatigue scores were similar to the baseline scores through 24 weeks of treatment, although the fatigue level seemed to increase during the treatment period and to return to baseline during the 2 weeks off, suggesting a mild and reversible treatment effect on fatigue (Fig 5).

Assessment of Plasma SU11248 Levels and Biomarkers

Patients achieved and maintained steady-state trough plasma concentrations (C_{min}) of SU11248 and its active metabolite throughout the dosing periods for multiple cycles. Median C_{min} (SU11248 and SU12662 combined) in all patients was 84.3 ng/mL, which is within the range of 50 to 100 ng/mL shown to inhibit target receptor tyrosine kinases in preclinical models.[19] Accumulation of study drug or its active metabolite was not observed across dosing cycles.

Table 2. Selected Treatment-Related Adverse Events of Interest and Laboratory Abnormalities by Grade Occurring in at Least 5% of Patients (n = 63)

Adverse Event	Grade 2		Grade 3		Grade 4		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Treatment-related adverse events								
Fatigue	17	27	7	11	0	0	24	38
Diarrhea	13	21	2	3	0	0	15	24
Nausea	10	16	2	3	0	0	12	19
Dyspepsia	10	16	0	0	0	0	10	16
Stomatitis	11	17	1	2	0	0	12	19
Vomiting	6	10	2	3	0	0	8	13
Constipation	8	13	0	0	0	0	8	13
Ejection fraction decline*	6	9	1	2	0	0	7	11
Anorexia	4	6	0	0	0	0	4	6
Dermatitis	4	6	1	2	0	0	5	8
Hypertension	2	3	1	2	0	0	3	5
Laboratory abnormalities								
Lymphopenia	25	40	20	32	0	0	45	72
Neutropenia	20	32	7	11	1	2	28	45
Anemia	17	27	5	8	1	2	23	37
Hyperlipasemia	2	3	12	19	1	2	15	24
Thrombocytopenia	11	18	0	0	0	0	11	18
Creatinine	9	14	0	0	0	0	9	14
Creatine kinase	7	11	1	2	1	2	9	15
Hyperamylasemia	1	2	5	8	0	0	6	10
Hepatic transaminase	3	5	2	3	0	0	5	8
Total bilirubin	3	5	0	0	0	0	3	5

*On two or more assessments of cardiac function.

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