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Phase II Study of Nilotinib in Melanoma Harboring KIT Alterations Following Progression to Prior KIT Inhibition

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Abstract

Purpose—Although durable responses can be achieved with tyrosine kinase inhibitors such as imatinib in melanomas harboring KIT mutations, the efficacy of alternative inhibitors after progression to imatinib and the activity of these agents on brain metastases is unknown.

Experimental Design—We conducted a phase II study of nilotinib 400 mg BID in two cohorts of patients with melanomas harboring KIT mutations or amplification: A) those refractory or intolerant to a prior KIT inhibitor; and B) those with brain metastases. The primary endpoint was 4-month disease control rate. Secondary endpoints included response rate, time-to-progression and

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overall survival. A Simon two-stage and a single-stage design was planned to assess for the primary endpoint in Cohorts A and B, respectively.

Results—Twenty patients were enrolled and 19 treated (11-Cohort A; 8-Cohort B). Three patients on Cohort A (27%; 95% CI, 8% – 56%) and 1 on Cohort B (12.5%; 90% CI, 0.6% – 47%) achieved the primary endpoint. Two partial responses were observed in Cohort A (18.2%, 90% CI, 3% – 47%); none were observed in Cohort B. The median time-to-progression and overall survival was 3·3 (90% CI, 2.1 – 3.9 months) and 9.1 months (90% CI, 4.3 – 14.2 months), respectively, in all treated patients.

Conclusion—Nilotinib may achieve disease control in patients with melanoma harboring KIT alterations and whose disease progressed after imatinib therapy. The efficacy of this agent in KIT altered melanoma with brain metastasis is limited.

Keywords

Melanoma; KIT; Mucosal; Acral

INTRODUCTION

Alterations in the *KIT* proto-oncogene define one unique molecular subset of melanoma. Mutations and amplification of *KIT* are observed in 3% of all melanomas, and are more common in disease arising from mucosal, acral or chronically sun-damaged surfaces.(1) The mutations identified are, in most cases, substitution mutations mutually exclusive of BRAF and NRAS mutations and often affect the juxtamembrane or kinase domains of KIT, leading to constitutive activation of KIT tyrosine kinase activity.

The clinical activity of KIT inhibition in those melanomas driven by KIT alterations has been reported in patients treated with agents such as imatinib,(2–4) dasatinib,(5) sorafenib,(6) and sunitinib,(7) with efficacy observed in prospective trials of imatinib(8–10) and sunitinib.(11) Despite the clinical benefit achieved with KIT inhibition in select patients with melanoma harboring KIT mutations, most patients ultimately experience disease progression. Failure of these agents has been observed within the brain,(12) which may be related to the frequent development of brain metastases in patients with advanced melanoma, as well as the limited central nervous system (CNS) penetration of many small molecule kinase inhibitors.

Secondary resistance to KIT inhibition in patients with gastrointestinal stromal tumors (GIST), a disease characterized by activating deletions or insertions in *KIT*, is caused primarily by the development of secondary KIT mutations commonly affecting the tyrosine kinase domains.(13) There can additionally be outgrowth of resistant subclones present at baseline that are selected during KIT inhibitor therapy. In GIST, the use of alternative KIT tyrosine kinase inhibitors after progression on imatinib, including sunitinib,(14) sorafenib,(15) and regorafenib,(16) has proven beneficial; however, the efficacy of sequential KIT inhibitors in melanoma is unknown.

Nilotinib (Tasigna®, AMN107) is a tyrosine kinase inhibitor structurally derived from imatinib that is approved in the United States for the treatment of chronic and accelerated

phase Philadelphia chromosome positive chronic myelogenous leukemia in patients resistant or intolerant to prior therapy with imatinib. Nilotinib binds to and inhibits the kinase domain of ABL/BCR-ABL and of the DDR, KIT, PDGF and several EPH receptor kinases with greater potency than imatinib,(17, 18) and maintains activity against a range of exon 9, 11 and 13 KIT mutations.(19) We conducted a phase II trial of nilotinib in patients with melanoma harboring KIT aberrations who experienced disease progression or intolerance to a prior KIT inhibitor. Given the frequent complication of brain metastases in patients with this disease and the potential for second-generation inhibitors of KIT to have activity within the CNS,(20) a cohort of patients with brain metastases was included.

MATERIALS AND METHODS

Study Design and Objectives

The primary objective was to assess the efficacy of nilotinib in patients with metastatic melanoma arising from acral, mucosal or chronically sun-damaged surfaces characterized by mutations or amplification of KIT after demonstration of disease progression or intolerance to a prior KIT tyrosine kinase inhibitor. Secondary objectives included efficacy assessment of nilotinib in patients with advanced KIT-mutant melanoma and CNS metastases. Tumor samples from all patients were prospectively tested for KIT mutation or amplification by quantitative polymerase chain reaction (PCR) or fluorescence *in situ* hybridization (FISH) as previously described.(8, 10)

Patients who met eligibility criteria received nilotinib 400 mg by mouth twice daily. Safety evaluations, including clinical and laboratory assessments, were conducted at baseline, every week for four weeks, every two weeks for four weeks, every four weeks for 28 weeks, and then every three months subsequently. Adverse event severity was graded using the NCI Common Terminology Criteria for Adverse Events, v3.0. Tumor response was measured radiographically every eight weeks for 32 weeks and every 12 weeks subsequently using RECIST 1.0 criteria, and included brain imaging for those with CNS involvement. Patients remained on study until the time of progression or the development of unacceptable toxicity not manageable with dose modification.

The primary endpoint was the proportion of patients who were alive and without progression of disease four months after beginning treatment with nilotinib. Secondary endpoints included best overall response rate (BORR), time-to-progression (TTP), overall survival (OS), and tolerability.

Patients

Patients were enrolled from eight academic medical centers between January 23, 2009 and June 14, 2011. Eligible patients had advanced melanoma harboring a KIT mutation or amplification and arising from acral, mucosal or chronically sun-damaged surfaces, as documented by the presence of solar elastosis. Patients without CNS metastases were enrolled onto Cohort A and must have experienced disease progression or intolerance to one or more KIT tyrosine kinase inhibitors. Intolerance was defined as drug discontinuation due to grade-2 events persisting for one month or longer, or any grade-3 or grade-4 rash, fluid

retention, cardiopulmonary events, thrombocytopenia, liver function abnormalities, or diarrhea that persisted despite optimal supportive care measures. Patients with measureable CNS disease harboring a KIT mutation were enrolled onto Cohort B and did not require prior therapy for eligibility. For those who received prior radiotherapy for CNS disease, progression was required in previously treated lesions or new lesions must have developed.

Other key inclusion criteria included age greater than 18 years; life expectancy greater than three months; Eastern Cooperative Oncology Group performance status of zero, one, or two; measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) v1.0; and adequate organ function. Exclusion criteria included prior therapy with nilotinib and clinically significant heart disease. All patients provided written-informed consent before initiating study procedures. The study was reviewed and approved by IRBs at all participating centers.

Trial Design

Cohort A employed an optimal Simon, two-stage design with 87% power to compare a null DCR of 5% with an alternative of 25%, with a one-sided type-I error of 7.5%. The target sample size was 28 patients, of whom 25 were expected to be evaluable for outcome. In the first stage, 13 evaluable patients would be assessed. If 2 or more patients achieved four-month disease control, an additional 12 evaluable patients would be assessed in the second stage. If 3 or more of 25 achieved four-month disease control, then nilotinib would be considered promising in this disease setting. A second feasibility cohort of 10 patients (Cohort B) was added after the study began to estimate the four-month DCR in patients with advanced, KIT-mutated melanoma and CNS metastases. Nilotinib would be of interest in this cohort if at least 2 of 10 patients achieved four-month disease control.

Statistical Methods

Baseline patient characteristics and adverse events were summarized using descriptive methods. Adverse events were reported as the most severe manifestation of each event category during any cycle of treatment. Four-month disease control rate (DCR) was defined as the proportion of treated patients with a complete or partial response (PR), or stable disease (SD) per RECIST 1.0 after 4 months of therapy. Best overall response rate (BORR) was defined as the proportion of treated patients with either complete or partial response (per RECIST) as best response to therapy. The number of treated patients in each cohort was the denominator for estimates of DCR and BORR. Time-to-progression (TTP) was defined as the time from initiation of nilotinib to the date of progression or last follow-up. Overall survival (OS) was defined as the time from initiation of nilotinib to the date of death or last follow-up. Four-month DCR and best overall response rates (BORR) are presented with 90% exact binomial confidence intervals. TTP and OS are presented using the method of Kaplan-Meier, with point-wise 90% confidence intervals estimated using log(−log(survival)) methodology.

Role of the Funding Source

Dr. Hodi developed the original study design and was responsible for the IND. Novartis provided investigational drug in addition to funding, and was involved in study design which

was developed in conjunction with the authors. The study sponsor had no role in the data collection, the data analysis, data interpretation, writing of the report, or the decision to submit for publication.

RESULTS

Patient Characteristics

Twenty patients were enrolled (11 in Cohort A and 9 in Cohort B) and 19 treated on this study (11 in Cohort A and 8 in Cohort B). One patient who enrolled in Cohort B withdrew consent before receiving study therapy. With the completion of a series of studies of imatinib and other agents targeting KIT in patients with melanoma harboring KIT alterations, enrollment to second-line trials became increasingly challenging and enrollment to this trial was closed prior to completion of either the first stage of the two-stage trial or the CNS feasibility component. The design for Cohort A was modified to a single-stage design with 11 patients, with 87% power to compare a null DCR of 5% with an alternative of 39.5%, using an exact binomial test and a one-sided type-I error of 7.5%.

Baseline patient characteristics of the 19 treated patients are shown in Table 1. Patients were predominantly female (74%), with a median age of 67 years (range, 38 – 85 years). Twelve (63%) patients had mucosal melanoma, four (21%) had acral melanoma, and three (16%) had melanoma arising from chronically sun-damaged skin (CSD). All patients had locoregionally advanced (5%) or distant disease (95%); most patients received one or more prior therapies. Sixteen patients received prior imatinib, one received both sorafenib and imatinib (patient 2), and three received prior ipilimumab therapy. All patients previously treated with a KIT inhibitor experienced progression on those agents and were not enrolled onto this study due to intolerance of prior therapy. Six of the 8 patients treated on Cohort B received prior therapy with imatinib, and 2 patients were naïve to KIT inhibition. Patient demographic and disease characteristics were similar between Cohorts A and B.

Tumor from the 19 treated patients was tested for the presence of KIT mutations, with 17 harboring such alterations (Tables 2 and 3). The specific mutations identified included exon 11 L576P (n = 4), exon 11 V560D (n = 1), exon 11 V560E (n = 1), exon 11 W557R (n = 1), exon 11 V559C (n = 1), exon 11 WKVVE 557–561 (n = 1), exon 13 K642E (n = 3), exon 13 Y646D (n = 1), exon 17 D820Y (n = 1), exon 17 N822K (n = 1), and exon 18 L831P (n = 1). One patient had tumor harboring two exon 13 mutations (R634Q and K642E). KIT amplification was tested in 12 cases, with 8 found to harbor such alteration. Two cases harbored amplification without a concurrent KIT mutation.

At the time of data analysis, 18 of the 19 treated patients were off-study, 14 of whom due to progressive disease. Median follow-up was 16.2 months in Cohort A (90% CI, 6.9 – 37.5 months) and 11.7 months in Cohort B (90% CI, 2.1 months − ∞).

Toxicity

Adverse events classified as possibly, probably or definitely related to nilotinib are shown in Supplemental Table 1. Events that were recorded multiple times for any patient are reported only once according to the worst grade. Although nilotinib was generally well-tolerated, 17

of the 19 patients treated reported adverse events, with fatigue (26%) and low-grade musculoskeletal and gastrointestinal discomfort (32%) most commonly observed. Grade-3 toxicities were observed in 4 patients, and included rash (n = 1), elevated pancreatic enzymes (n = 2), and transaminitis and hyponatremia (n = 1). Grade 3 toxicity was managed by dose reduction to 400 mg QD (n = 2) or dose delay followed by reinitiation of treatment at 400 mg BID (n = 2). No patient experienced grade-4 related adverse events. Toxicity rates and patterns were comparable for Cohorts A and B.

Clinical Activity

Four-Month Disease Control Rate. In Cohort A, three of 11 patients were alive without disease progression at four months (27%; 90% CI, 8% – 56%), a proportion significantly greater than the DCR of 5% ($p = 0.03$) assumed under the null hypothesis. Based on three observed responses, there is sufficient evidence to conclude that nilotinib would have been considered worthy of further study in Cohort A based on the initial two-stage design. In Cohort B, one of eight treated patients achieved disease control at four months (12.5%; 90% CI, 0.6% – 47%), with no evidence that four-month DFR is greater than 5% in this population.

Response Rate—Of the 19 patients treated, four were inevaluable for radiographic response to therapy in non-CNS lesions. In Cohort A, patient 11 initiated therapy but subsequently underwent resection of abdominal disease due to tumor-associated gastrointestinal bleeding. In Cohort B, patient 16 initiated therapy but developed rapid clinical decline due to progressive leptomeningeal disease and withdrew consent for further treatment and evaluation. Patients 15 and 17 presented with CNS-only disease, without measurable lesions in extra-cranial sites.

In Cohort A, two partial responses were observed (18.2%, 90% CI, 3% – 47%). One partial response was observed in an 81 year-old female with advanced vulvar melanoma harboring an exon 11 L576P mutation without concurrent amplification (Patient 3). She previously achieved a durable partial response to therapy with imatinib lasting 12.4 months and has an ongoing response to nilotinib at 37.5 months. Additional patients achieved minor responses to therapy (Tables 2 and 3).

Of the eight patients treated on Cohort B, seven were evaluable for response in CNS metastases which either were not previously treated with radiotherapy or which demonstrated progression following treatment (Figure 1). Assessing CNS lesions only, we observed one PR (12.5%, 90% CI 0.6% – 47%) lasting 3.9 months (Patient 4) and one minor response (Patient 15), each in patients not previously treated with a KIT inhibitor. The PR was observed in a 48 year-old female with mucosal melanoma arising from the anorectal region harboring an exon 11 V560D mutation without concurrent amplification. A brain MRI performed 5 months after receiving stereotactic radiosurgery to left temporal, left parietal, right frontal, and right mid-cerebellar lesions demonstrated the development of progression in the previously treated lesions and the development of numerous infra and supratentorial hemorrahgic brain metastases (Figure 1A). She achieved a minor response in her extracranial metastases (20% tumor regression by RECIST criteria) and a partial

response in her target brain metatases (36% regression by RECIST criteria) as demonstrated by the circled lesions in Figures 1A and 1B. Despite durable stability in her extracranial disease after four months of therapy and further reduction in the size of several of the brain metastases, there was progression in non-target brain metastases and she was taken off study.

Time-to-Progression—The time-to-progression achieved with nilotinib as well as to a prior KIT inhibitor, if applicable, is shown by patient in Figure 2. The median TTP was 3.4 months (90% CI, 0.9 – 5.5 months) and 2.6 months (90% CI, 1.8 – 3.9 months; Figure 3A) in Cohorts A and B, respectively.

Overall Survival—Eleven patients (57.9%) were deceased at the time of data analysis, with one patient lost to follow-up. The median OS in Cohort A was 14.2 months (90% CI, 7.1 months − ∞) and was longer than observed in Cohort B (4.3 months; 90% CI, 3.5 – 11.9 months; p = 0.05; Figure 3B).

DISCUSSION

These results demonstrate that a subset of patients with melanomas harboring genetic alterations of KIT may benefit from nilotinib after experiencing disease progression to a prior KIT inhibitor. Three of 11 patients without brain metastasis achieved disease control at four months with nilotinib, with observed progression-free survival times of 5.5, 11.5, and 37.5+ months. Notably, patients 3 and 20 achieved a durable PR and CR, respectively, to imatinib lasting 12.4 and 20 months, respectively, before achieving durable PRs to nilotinib, demonstrating that nilotinib can overcome the development of secondary resistance to imatinib. Based on the original study design for Cohort A which required three or more patients to achieve disease control at four months, the primary endpoint of four-month DCR was achieved.

Given the high incidence of brain metastases in melanoma and the potential efficacy of second-generation KIT inhibitors in CNS metastases,(20) we included an exploratory cohort of patients with brain metastases from melanoma harboring KIT alterations. Although available data suggests the limited penetration of nilotinib within the CNS, clinical activity has been observed in the brain in BCR-ABL positive leukemia(21). Such efficacy may be explained by the high protein-binding affinity of nilotinib coupled with the low protein concentration within the cerebrospinal fluid, thus resulting in relatively higher amounts of free nilotinib within the CNS. Indeed, of seven patients in our trial evaluable for response in brain lesions, one achieved a 36% reduction and another achieved a 25% reduction in the CNS tumor burden with therapy. A mixed response in the brain lesions was observed in some cases, with clear reduction in the size of several brain metastases and unambiguous progression in others. While anecdotal, these variable responses may suggest more prominent intra-tumoral molecular heterogeneity in CNS lesions when compared to disease in other organs or variable pharmacologic penetration into the brain metatases. Of note, both patients who achieved radiographic responses within the brain were not previously treated with a KIT inhibitor such as imatinib. Despite the radiographic changes observed, the progression-free and overall survival in this cohort of patients were short.

The greater potency of nilotinib over imatinib against the mutant KIT oncoprotein provides pharmacologic rationale for using nilotinib.(18, 22) Furthermore, the sensitivity of specific *KIT* mutations to clinically available inhibitors can differ, with some mutations affecting the binding affinity of specific inhibitors of KIT as previously demonstrated in *in vitro* and clinical studies of GIST.(13, 19, 23) Although preliminary evidence of activity with nilotinib in patients with melanoma harboring KIT alterations not previously treated with a KIT inhibitor has been observed, with two partial responses lasting 8.4 and 10+ months reported in nine patients with melanoma harboring a KIT alteration not previously treated with a KIT inhibitor,(24) whether nilotinib is superior to imatinib in KIT-inhibitor naïve patients with melanoma is unknown. In advanced GIST, nilotinib was not superior to imatinib as first-line therapy and did not improve outcomes when compared with best-supportive care in the third-line setting.(25, 26) Importantly, mechanisms of secondary resistance in GIST, which commonly involve the development of secondary *KIT* mutations affecting the tyrosine kinase domains in exons 13 and 17,(27–29) appear to differ from those observed in melanoma driven by KIT alterations. Thus far, no such secondary mutations have been observed in KIT melanoma. Rather, the limited data available suggests that, in melanoma, the development of secondary NRAS mutations(11) and activation of the mTOR pathway by alternative mechanisms may result in secondary resistance.(30)

In conclusion, the use of nilotinib in a subset of patients with melanoma harboring KIT alterations previously treated with an inhibitor of KIT can result in clinical benefit, although efficacy of this agent in brain metastasis is limited. Although this trial is underpowered to conclude clinical benefit, the data suggest further studies of sequential KIT inhibitor therapy for this molecular subset of patients is warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STATEMENT OF TRANSLATIONAL RELEVANCE

Although significant clinical benefit can be achieved with KIT inhibition in a subset of patients with melanoma driven by activating alterations in KIT, the development of secondary resistance is common. In this phase II study of nilotinib 400 mg BID, three of 11 patients with melanomas harboring KIT mutations or amplification who were refractory to a prior KIT inhibitor had disease control lasting 4 months or greater, with 2 achieving a partial response to therapy. One of 8 patients with melanomas metastatic to the brain harboring KIT mutations or amplification had disease control lasting 4 months or greater, with none achieving a radiographic response. We conclude that nilotinib can achieve disease control in a subset of patients with melanoma harboring KIT alterations after progression on a prior tyrosine kinase inhibitor; however, the efficacy of this agent in KIT altered melanoma with brain metastasis is limited.

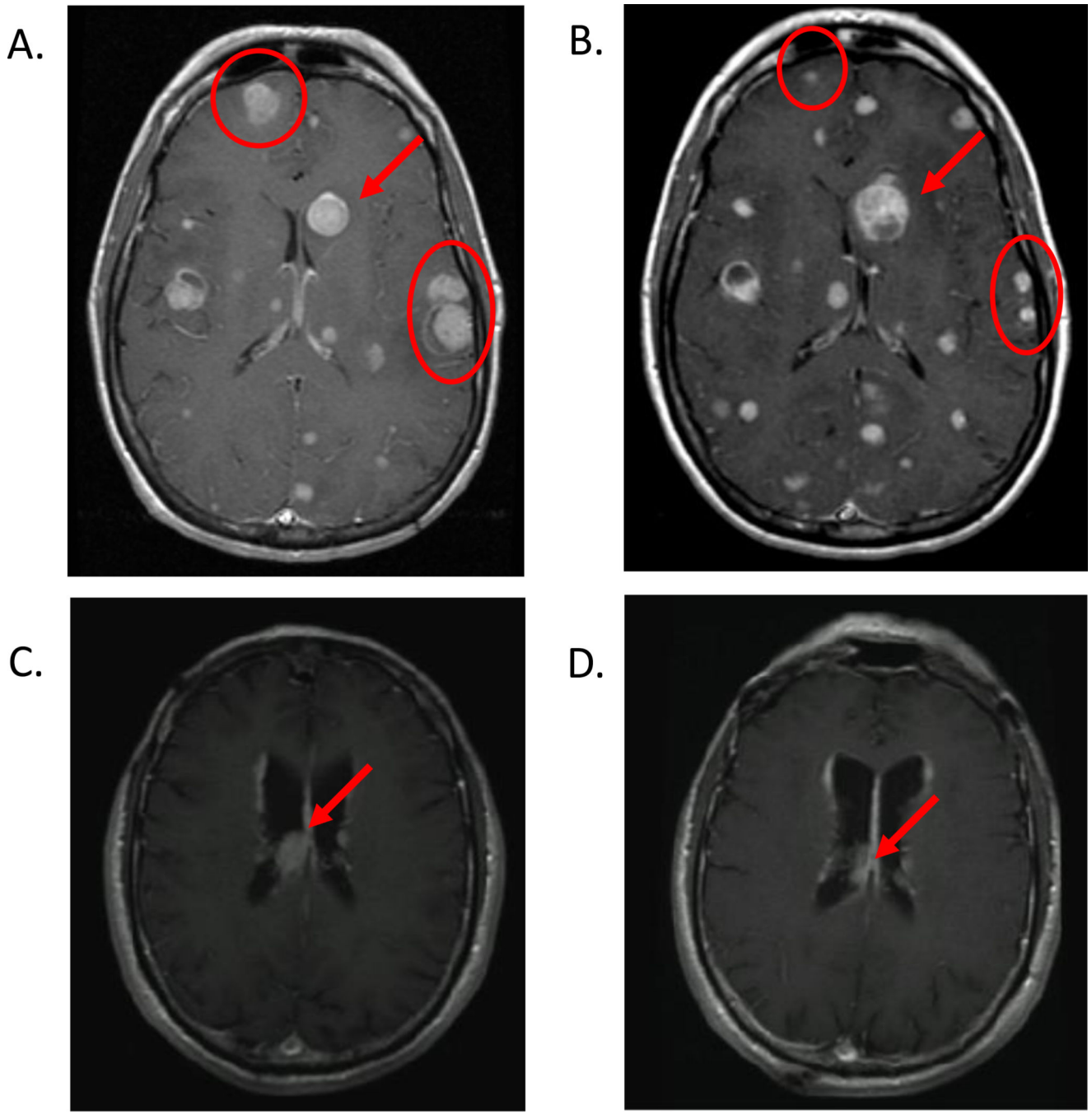

Figure 1.

Representative images from two patients achieving radiographic responses in brain metastases with nilotinib. Magnetic resonance images of brain metastases present at baseline (Figure 1A) and after 4 months of therapy (Figure 1B) in a patient who achieved a minor response in extracranial metastases and a partial response in target brain metatases as demonstrated by the circled lesions are presented. The baseline brain MRI was performed 5 months after receiving stereotactic radiosurgery to left temporal, left parietal, right frontal, and right mid-cerebellar lesions and demonstrate the development of progression in the

previously treated lesions and the development of numerous new infra and supratentorial hemorrahgic brain metastases (Figure 1A). Despite durable stability in the extracranial disease after 4 months of therapy and further reduction in the size of several of the brain metastases, there was progressing in non-target brain metastases (arrow). Magnetic resonance images of a brain metastasis present at baseline (Figure 1C) and after 2 months of therapy (Figure 1D) in a patient who achieved a partial response in a solitary brain metastases are presented. No prior radiotherapy or surgery was performed in this patient prior to initiation of study therapy.

Study Subject #	KIT Mutation	KIT Amplification
1	Exon 17 D820Y	Present
2	Exon 13 K642E	Present
3	Exon 11 L576P	Not Present
4	Exon 11 V560E	Not Present
5	None	Present
6	Exon 11 W577R	Not Present
7	None	Present
8	Exon 17 N822K	Present
9	Exon 13 R643Q and K642E	Not tested
10	Exon 11 V560D	Not tested
11	Exon 11 V559C	Present
12	Exon 11 L576P	Present
13	Exon 11 WKVVE 557-561	Not tested
14	Exon 13 K642E	Not tested
15	Exon 11 L576P	Not tested
16	Exon 13 Y646D	Not tested
17	Exon 18 L831P	Not present
18	Exon 11 L576P	Not tested
20	Exon 13 K642E	Present

* - Although patients 6 and 9 received prior imatinib, the duration of imatinib therapy is not known.

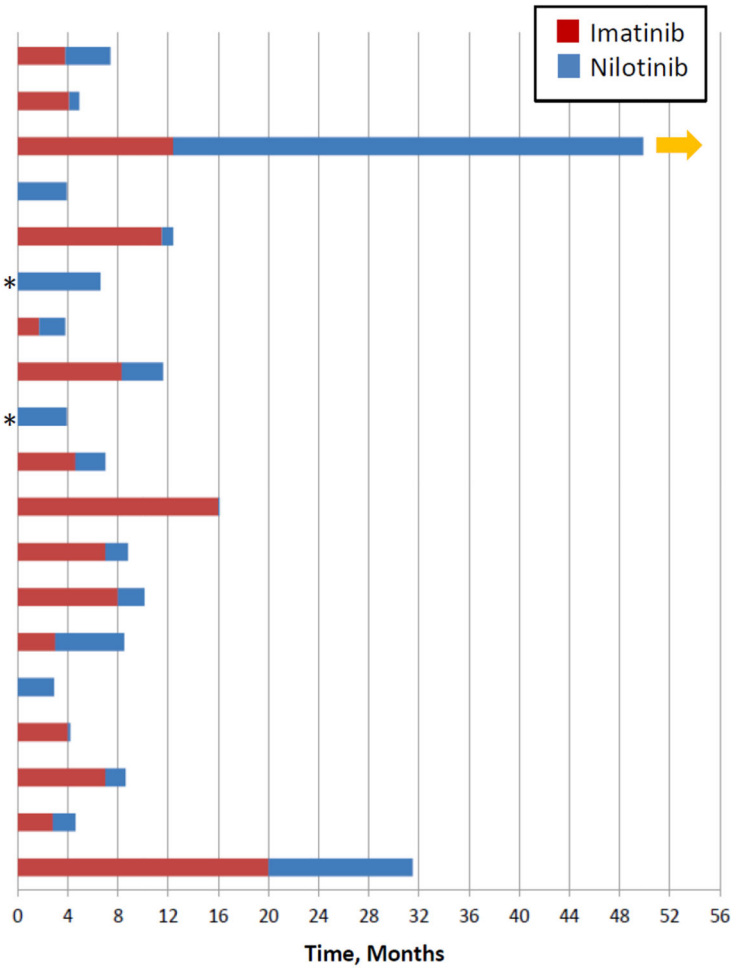

Figure 2.
Treatment Response Over Time to Imatinib and Nilotinib by Genetic Alteration of KIT.

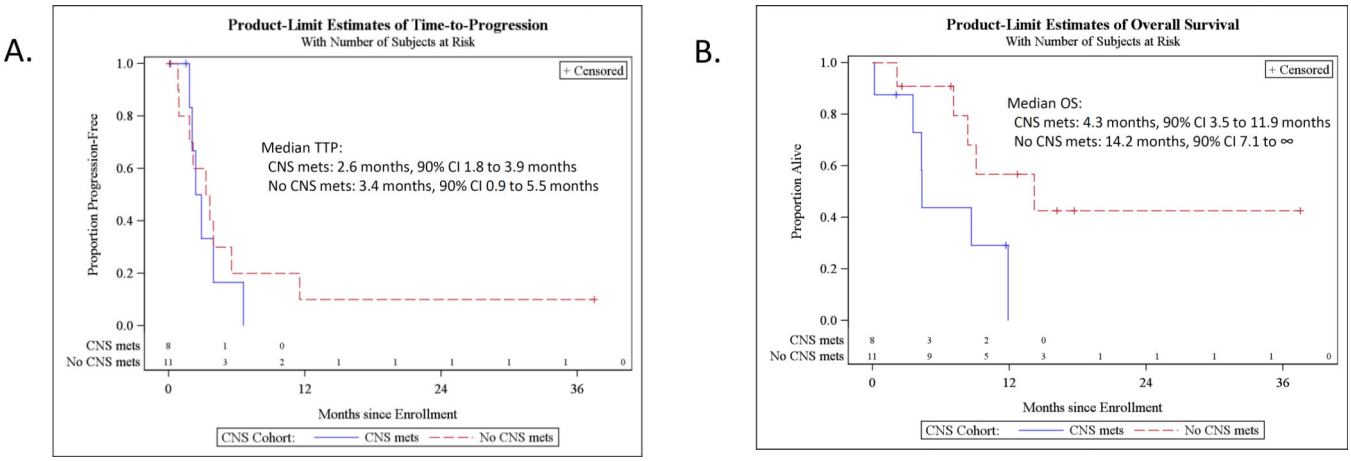

Figure 3.

Time-to-Progression and Overall Survival. Kaplan-Meier estimates of time-to-progression (Figure 3A) and overall survival (Figure 3B) in those enrolled on Cohorts A (dotted red lines) and B (solid blue line) are shown. The vertical lines indicate that patients' data were censored. The median time-to-progression was 3·4 months (90% CI, 0·9 – 5·5) in Cohort A and 2·6 months (90% CI, 1·8 – 3·9) in Cohort B. Overall survival was 14·2 months [90% CI, 7·1 – ∞] in Cohort A and 4.3 months [90% CI, 3·5 – 11·9] in Cohort B.

Table 1

Patient characteristics for patients who received at least 1 dose of study therapy.

	Overall Population (n = 19)	Cohort A (n = 11)	Cohort B (n = 8)
Age in Years, Median (Range)	67.0 (38.0 – 85.0)	68.0 (55.0 – 82.0)	60.0 (38.0 – 85.0)
Gender			
Male (%)	5 (26.3%)	2 (18.2%)	3 (37.5%)
Female (%)	14 (73.7%)	9 (81.8%)	5 (62.5%)
Race			
Caucasian (%)	16 (84.2%)	10 (90.9%)	6 (75.0%)
Black/African American (%)	1 (5.3%)	1 (9.1%)	0 (0%)
Other (%)	2 (10.5%)	0 (0%)	2 (25.0%)
Ethnicity			
Hispanic or Latino (%)	3 (15.8%)	1 (9.1%)	2 (25.0%)
Non-Hispanic (%)	10 (52.6%)	7 (63.6%)	3 (37.5%)
Not Reported (%)	6 (31.6%)	3 (27.3%)	3 (37.5%)
Clinical Melanoma Subtype			
Acral	4 (21.0%)	2 (18.2%)	2 (25.0%)
Mucosal	12 (63.2%)	7 (63.6%)	5 (62.5%)
Chronically Sun-Damaged Skin	3 (15.8%)	2 (18.2%)	1 (12.5%)
ECOG * Performance Status			
0 (%)	11 (57.9%)	7 (63.6%)	4 (50.0%)
1 (%)	8 (42.1%)	4 (36.4%)	4 (50.0%)
2 (%)	0 (0%)	0 (0%)	0 (0%)
Stage			
III (%)	1 (5.3%)	1 (9.1%)	0 (0%)
IV (%)	18 (94.7%)	10 (90.9%)	8 (100%)
Elevated Lactate Dehydrogenase † (%)	8 (42.1%)	5 (45.5)	3 (37.5%)
Number of Prior Systemic Therapies, Median (Range)	2 (0 – 5)	2 (1 – 4)	2 (0 – 5)
Imatinib (%)	17 (89.5%)	11 (100%)	6 (75.0%)
Sorafenib (%)	1 (5.3%) ^	1 (9.1%)	0 (0%)
Other Kinase Inhibitor (%)	0 (0%)	0 (0%)	0 (0%)
Ipilimumab (%)	3 (15.8%)	1 (9.1%)	2 (25.0%)

* ECOG denotes Eastern Cooperative Oncology Group

† Value exceeding 280 U/L

^ Patient 2 received both sorafenib and imatinib.

Table 2

Clinical melanoma subtype, associated KIT alterations, clinical response to prior therapy with a KIT inhibitor and clinical response to nilotinib in those without CNS involvement (Cohort A).

Study Subject #	Melanoma Subtype	KIT Mutation	KIT Amplification	Prior KIT Inhibitor[+]	RECIST Response to Prior KIT Inhibitor	PFS to Prior KIT Inhibitor (Months)	RECIST Response to Nilotinib (Best Percent Response)	PFS to Nilotinib (Months)
1	Mucosal	Exon 17 D820Y	Present (qPCR)	Imatinib	PR	3.8	SD (−26%)	3.6
2[x]	Acral	Exon 13 K642E	Present (FISH)	Imatinib	uPR	4.1	PD (6%)[*]	0.8
3	Mucosal	Exon 11 L576P	Not Present (FISH)	Imatinib	PR	12.4	PR (−59%)	37.5[+]
5	Mucosal	None	Present (qPCR)	Imatinib	SD	11.5	Clinical PD	0.9
8	CSD	Exon 17 N822K	Present (FISH)	Imatinib	SD	8.3	SD (0%)	3.3
9	Mucosal	Exon 13 R643Q and K642E	Not tested	Imatinib	Unk	Unk	SD (14%)	3.9
11	CSD	Exon 11 V559C	Present (FISH)	Imatinib	SD	16	Ineval	0.1
12	Mucosal	Exon 11 L576P	Present (qPCR)	Imatinib	PR	7	Clinical PD	1.8
13	Acral	Exon 11 WKVVE 557–561	Not tested	Imatinib	SD	8	PD[*] (18%)	2.1
14	Mucosal	Exon 13 K642E	Not tested	Imatinib	SD	3	SD (−22%)	5.5
20	Mucosal	Exon 13 K642E	Present (qPCR)	Imatinib	CR	20	PR (−54%)	11.5

Abbreviations: qPCR – quantitative polymerase chain reaction

[+]- All patients previously treated with a KIT inhibitor experienced progression on those agents and were not enrolled onto this study due to intolerance of prior therapy

[x] – Patient 2 also received sorafenib; however, his response to this therapy is not known.

* - Signifies the development of progression in non-target lesions or the development of new lesions

Table 3

Clinical melanoma subtype, associated KIT alterations, clinical response to prior therapy with a KIT inhibitor and clinical response to nilotinib in those with CNS involvement.

Study Subject #	Melanoma Subtype	KIT Mutation	KIT Amplification	Prior KIT Inhibitor[+]	RECIST Response to Prior KIT Inhibitor	PFS to Prior KIT Inhibitor (Months)	RECIST Response to Nilotinib in non-CNS Lesions (Best Percent Response)	RECIST Response to Nilotinib in CNS Lesions (Best Percent Response)	PFS to Nilotinib (Months)
4	Mucosal	Exon 11 V560D	Not Present (FISH)	None	n/a	n/a	SD (−20%)	PR (−36%)[*]	3.9
6	Acral	Exon 11 W577R	Not Present (FISH)	Imatinib	Unk	Unk	SD (−23%)	SD[a] (11%)	6.6
7	Acral	None	Present (qPCR)	Imatinib	PD	1.7	SD (3%)	PD (37.5%)	2.1
10	Cutaneous	Exon 11 V560D	Not tested	Imatinib	PR	4.6	PD (44%)	PD (40%)	2.4
15	Mucosal	Exon 11 L576P	Not tested	None	n/a	n/a	n/a[b]	SD (−25%)	2.9
16	Mucosal	Exon 13 Y646D	Not tested	Imatinib	SD	~ 4	Uneval	Uneval	0.2
17	Mucosal	Exon 18 L831P	Not Present (FISH)	Imatinib	SD	~ 7	n/a[b]	SD (9%)	1.6
18	Mucosal	Exon 11 L576P	Not tested	Imatinib	SD	2.8	SD (14%)	PD (0%)[*]	1.8

Abbreviations: Unk – Unknown

[+] - All patients previously treated with a KIT inhibitor experienced progression on those agents and were not enrolled onto this study due to intolerance of prior therapy

[*] - Signifies the development of progression in non-target lesions or the development of new lesions

[a] – Patient 6 underwent resection of one symptomatic brain target lesion 1.6 months after initiation of therapy; a second CNS target lesion remained stable for 6.6 months after initiation of therapy; however, new CNS lesions were noted at that time and the patient was taken off for POD

[b] - No non-CNS lesions present.