ORIGINAL RESEARCH

Efficacy and safety of ripretinib in patients with *KIT*-altered metastatic melanoma

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Background: Ripretinib, a broad-spectrum KIT and platelet-derived growth factor receptor A switch-control tyrosine kinase inhibitor, is approved for the treatment of adult patients with advanced gastrointestinal stromal tumor as $\geq$ fourth-line therapy. We present the efficacy and safety of ripretinib in patients with *KIT*-altered metastatic melanoma enrolled in the expansion phase of the ripretinib phase I study.

Patients and methods: Patients with *KIT*-altered metastatic melanoma were enrolled and treated with ripretinib at the recommended phase II dose of 150 mg once daily in 28-day cycles. Investigator-assessed responses according to Response Evaluation Criteria In Solid Tumors version 1.1 were carried out on day 1 of cycles 3, 5, 7, every three cycles thereafter, and at a final study visit.

Results: A total of 26 patients with *KIT*-altered metastatic melanoma (25 with *KIT* mutations, 1 with *KIT*-amplification) were enrolled. Patients had received prior immunotherapy ($n = 23$, 88%) and KIT inhibitor therapy ($n = 9$, 35%). Confirmed objective response rate (ORR) was 23% [95% confidence interval (CI) 9%-44%; one complete and five partial responses] with a median duration of response of 9.1 months (range, 6.9-31.3 months). Median progression-free survival (mPFS) was 7.3 months (95% CI 1.9-13.6 months). Patients without prior KIT inhibitor therapy had a higher ORR and longer mPFS ($n = 17$, ORR 29%, mPFS 10.2 months) than those who had received prior KIT inhibitor treatment ($n = 9$, ORR 11%, mPFS 2.9 months). The most common treatment-related treatment-emergent adverse events (TEAEs) of any grade in $\geq$15% of patients were increased lipase, alopecia, actinic keratosis, myalgia, arthralgia, decreased appetite, fatigue, hyperkeratosis, nausea, and palmar-plantar erythrodysesthesia syndrome. There were no grade $\geq$4 treatment-related TEAEs.

Conclusions: In this phase I study, ripretinib demonstrated encouraging efficacy and a well-tolerated safety profile in patients with *KIT*-altered metastatic melanoma, suggesting ripretinib may have a clinically meaningful role in treating these patients.

Key words: KIT, melanoma, tyrosine kinase inhibitor, ripretinib

INTRODUCTION

KIT, a type III transmembrane tyrosine kinase receptor, plays a key role in normal melanocyte development, differentiation, proliferation, and survival.[1-3] *KIT* alterations (mutations or amplifications) are observed in ~3% of all melanomas and are most common in melanomas on mucosal membranes (ranges from 9% to 39%), acral skin (11%-36%), and chronically sun-damaged (CSD) skin (4%-28%).[4-8] *KIT* mutations in melanoma are heterogeneous and are observed in exons 9, 11, 13, 17, and 18.[4,5,9] KIT is an established therapeutic target in cancers with activating mutations of *KIT*, such as gastrointestinal stromal tumor (GIST) or systemic mastocytosis, and small molecule KIT inhibitors are approved for these diseases.[10-15] Ripretinib, a broad-spectrum KIT and platelet-derived growth factor receptor A (PDGFRA) switch-control tyrosine kinase inhibitor, is approved for the treatment of adult patients with advanced GIST as $\geq$ fourth-line therapy.[16,17] Ripretinib specifically binds both the switch pocket

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and the activation loop of the KIT and PDGFRA kinases, which locks them into an inactive state and prevents downstream signaling and cell proliferation.[18] The dual mechanism of action provides broad inhibition of KIT and PDGFRA kinase activity, allowing for the inhibition of activity in both wild-type KIT and PDGFRA kinases, as well as the inhibition of activity in KIT and PDGFRA mutants that are associated with drug-resistant GIST tumors.

KIT mutations in GIST most commonly occur on exons 11 and 9, accounting for ∼70% and ∼15% of tumors, respectively.[19] In GIST, of the single-point mutations identified in KIT exon 11, the most common mutations were V559D and L576P, with each mutation accounting for ∼30% of the KIT single-point mutations.[19] KIT mutations can also occur in exon 13 and exon 17, though these mutations are rare in GIST and are associated with resistance to KIT inhibition via imatinib.[20] Many of the KIT mutations that have been identified in melanomas also occur in the same exons that are altered in GIST, although the frequency of these mutations may be different. For example, compared with GIST, mutations in exon 13 and exon 17 occur more frequently, accounting for ∼20% and ∼10% of KIT mutations in melanomas, respectively. In a recent analysis of KIT mutations in 28 patients with mucosal melanoma, 7 patients had KIT mutations while 21 patients had wild-type KIT.[21] Of the KIT mutations assessed, the most frequent mutations were detected in exon 11 and exon 9, with each accounting for ∼42% of mutations. In another analysis that screened for KIT mutations in 189 melanoma patients, the most common mutation occurred in exon 11, accounting for ∼90% of KIT mutations detected.[9] In this study, the L576P point mutation of exon 11 accounted for 50% of KIT exon 11 mutations and 45% of all KIT mutations.[9] Considering the overlap in KIT mutations in GIST and melanoma, KIT inhibition has been studied as a therapeutic strategy in patients with metastatic melanoma harboring KIT alterations.[5,9] Previous studies assessing the efficacy of KIT inhibitors such as imatinib, sunitinib, dasatinib, and nilotinib in patients with KIT-altered metastatic melanoma have demonstrated clinical activity with an objective response rate (ORR) ranging between 16% and 30% and median progression-free survival (mPFS) of 3-6 months.[22,23] Currently, there are no approved KIT inhibitors for KIT-altered metastatic melanoma, and the National Comprehensive Cancer Network clinical practice guideline recommends specified KIT inhibitors as second-line therapy in certain situations.[24] Here, we report the efficacy and safety of a starting dose of ripretinib 150 mg once daily (QD) in patients with KIT-altered metastatic melanoma enrolled in the expansion phase of the ripretinib phase I study (NCT02571036).

PATIENTS AND METHODS

Patients, study design, and treatment

Patients were ≥18 years old with a histologically confirmed diagnosis of melanoma with mutations and/or amplification in KIT or PDGFRA; KIT alterations were assessed in archival tumor samples using clinical next-generation sequencing or PCR-based tests obtained as a part of clinical care. Other eligibility criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤2 with adequate organ function and bone marrow reserve. This was a multicenter phase I dose-escalation study of ripretinib with an expansion phase at the recommended phase II dose (RP2D) in multiple advanced malignancies (Clinicaltrials.gov Identifier: NCT02571036).[25] In the expansion phase of the phase I study, patients with KIT-altered metastatic melanoma were treated with ripretinib at the RP2D of 150 mg QD in repeated 28-day cycles until disease progression, unacceptable toxicity, or consent withdrawal. Patients who had disease progression at ripretinib 150 mg QD were allowed to dose escalate to 150 mg twice daily (BID) after the completion of cycle 2, at the investigator's discretion. Melanoma's were graded using TNM Staging for Melanoma.

Study objectives and assessments

The primary objectives of the expansion phase of the phase I study were assessments of the safety and efficacy of ripretinib. Secondary objectives included pharmacokinetic (PK) analysis of ripretinib. Routine clinical and laboratory assessments, physical examination, ECOG PS, echocardiograms/multigated acquisition scans, as well as dermatologic and ophthalmologic examinations were conducted at baseline and prespecified intervals. Adverse events were monitored continuously from the signing of the informed consent until 30 days after the last ripretinib dose and were graded by the investigators using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Efficacy was evaluated in patients with KIT-altered metastatic melanoma receiving a starting dose of ripretinib 150 mg QD. Tumor progression was assessed by the investigator using computed tomography/magnetic resonance imaging according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1) on day 1 of cycles 3, 5, 7, every three cycles thereafter, and at a final study visit. An ORR was defined as the proportion of patients with a confirmed complete response (CR) or confirmed partial response (PR). Responses were confirmed ∼28 days later and assessed by the investigator using RECIST v1.1. Other efficacy endpoints included time to response (defined as the time from cycle 1 day 1 to PR or CR), duration of objective response (time from a confirmed CR or PR to disease progression or death), and progression-free survival (PFS; defined as the time from cycle 1 day 1 to disease progression or death).

Pharmacokinetic methods. PK samples of all patients enrolled in the phase I study receiving ripretinib were analyzed at a central laboratory. Plasma steady-state trough concentrations (C_{trough}) of ripretinib, DP-5439 (an active metabolite of ripretinib), and ripretinib plus DP-5439 on cycle 1 day 15 were analyzed using a validated high-performance liquid chromatography-tandem mass spectrometric method.

Statistical analyses. Safety analyses were performed in all patients with *KIT*-altered metastatic melanoma who received a ripretinib dose (includes 150 mg QD and 150 mg BID period). PK analyses were performed on all patients in the safety analyses who had ≥1 PK concentration obtained. Among the patients who dose-escalated to ripretinib 150 mg BID after disease progression on 150 mg QD, PFS1 was the interval between the date of the first dose of ripretinib 150 mg QD to disease progression; PFS2 was the interval between the date of the first dose of ripretinib 150 mg BID to disease progression or death. Baseline demographics, patient characteristics, and PK parameters were summarized using descriptive statistics. ORR was summarized using two-sided 95% exact binomial confidence intervals (CIs). PFS was analyzed using the Kaplan-Meier method; duration of response was summarized descriptively for confirmed and non-confirmed responders.

Ethics. This study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization Guidelines for Good Clinical Practice. Patients provided written informed consent to participate in this study, and the protocol, protocol amendments, and informed consent documents were approved by institutional review boards/ethics committees at each study site and by appropriate regulatory authorities before the start of the study.

RESULTS

Patients and treatment exposure

From 25 October 2018 to 10 May 2021 (data cut-off), 26 patients with *KIT*-altered metastatic melanoma were enrolled and received ripretinib starting at 150 mg QD. Baseline characteristics are listed in Table 1. The median age was 66 years (range, 32-86 years), and patients were predominantly White (77%). Mucosal melanoma was the most frequent (*n* = 15, 58%), while four patients (15%) had an acral subtype. *KIT* mutations were observed in exon 11 (*n* = 9, 35%), exon 13 (*n* = 4, 15%), exon 17 (*n* = 11, 42%), and exon 18 (*n* = 1, 4%); *KIT*-amplification was reported in one patient. Most patients had stage IV disease (*n* = 24, 92%) and received prior immunotherapy (*n* = 23, 88%). Nine (35%) patients had received prior KIT inhibitor therapy, eight of whom were treated with imatinib either as a single agent or as combination therapy. The median number of prior anticancer therapy lines was 2.

At data cut off, nine (35%) patients remained on study treatment (eight on ripretinib 150 mg QD and one on ripretinib 150 mg BID; Supplementary Table S1 and Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100520). The median duration of treatment with ripretinib 150 mg QD was 4.4 months (range, 0.5-33.6 months) and five (19%) patients received ripretinib 150 mg QD for 12 months or longer (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2022.100520). The ripretinib dose was escalated to 150 mg BID after radiologic progression on 150

Table 1. Baseline characteristics in patients with *KIT*-altered metastatic melanoma receiving ripretinib

Characteristics	Ripretinib (*n* = 26)
Age, median (range), years	66 (32-86)
<65 years, *n* (%)	12 (46)
≥65 years, *n* (%)	14 (54)
Sex, *n* (%)	
Male	12 (46)
Female	14 (54)
Race, *n* (%)	
White	20 (77)
Black or African American	1 (4)
Asian	2 (8)
Other	3 (12)
ECOG performance status, *n* (%)	
0	8 (31)
1	16 (62)
2	2 (8)
Melanoma subtype, *n* (%)	
Mucosal	15 (58)
Acral	4 (15)
Desmoplastic	1 (4)
Spitzoid	1 (4)
Not otherwise specified	5 (19)
Disease stage, *n* (%)	
IIIC	1 (4)
IV	24 (92)
Missing	1 (4)
Prior anticancer therapy lines,[a] *n* (%)	
Median number of prior lines of therapy[b]	2
0	3 (12)
1	5 (19)
2	8 (31)
3+	10 (38)
Immunotherapy	23 (88)
KIT inhibitor[c,d]	9 (35)
***KIT* mutation status,[e] *n* (%)**	
Exon 11	9 (35)
Exon 13	4 (15)
Exon 17	11 (42)
Exon 18	1 (4)
KIT-amplification	1 (4)

ECOG, Eastern Cooperative Oncology Group.
[a]Prior immunotherapy included ipilimumab, nivolumab, and pembrolizumab as either single-agent therapy or as part of a combination therapeutic strategy.
[b]Prior combination therapies were counted as one-prior line of therapy.
[c]Patients received ≥1 KIT inhibitor: imatinib, imatinib plus ipilimumab, imatinib plus pembrolizumab, nilotinib, axitinib, and dasatinib plus crizotinib.
[d]Overall, eight patients received imatinib either as a single agent or as combination therapy.
[e]Tumor biopsy at screening or archival tumor sample allowed if no anticancer therapy was administered since sample collection.

mg QD in four (15%) patients. Based on sparse PK sampling (*n* = 21), the mean C_{trough} on cycle 1 day 15 for ripretinib, DP-5439 (an active metabolite of ripretinib), and ripretinib plus DP-5439 was 508 ng/ml, 1060 ng/ml, and 1590 ng/ml, respectively (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100520).

Efficacy

The best percentage change from the baseline sum of diameters in target lesions is shown in Figure 1A. The best overall response for all patients is listed in Tables 2 and 3. Among the 26 patients, the confirmed ORR was 23% (95% CI 9% to 44%; CR, *n* = 1 in acral; PR, *n* = 5: 4 in mucosal and 1 in acral), with a median duration of response of 9.1

months (range, 6.9-31.3 months) (Table 2). An additional 11 patients (42%) had stable disease for ≥6 weeks and 8 (31%) had progressive disease. One patient had an exon 11 and exon 17 compound mutation at study entry (Table 3). The best overall response for this patient was PR. The median PFS was 7.3 months (95% CI 1.9-13.6 months) (Figure 1B). There were two unconfirmed PRs in addition to the five confirmed PRs, resulting in an overall ORR of 31% (95% CI 14%-52%; CR, $n = 1$; PR, $n = 7$). Including the two unconfirmed PRs, the median duration of response was 8.7 months (range, 1.7-31.3 months).

Of note, a 53-year-old female who received four prior lines of systemic melanoma therapy before enrolling in this study did not have a follow-up imaging assessment due to early death. Her medical course was complicated by gastric hemorrhage, and she stopped ripretinib on cycle 1 day 15 due to respiratory failure secondary to pneumonia that resulted in her death; both events were unrelated to ripretinib treatment. Among the 25 patients with follow-up imaging assessments, the confirmed ORR was 24% (6/25; CR, $n = 1$; PR, $n = 5$), and confirmed plus unconfirmed ORR was 32% (8/25; CR, $n = 1$; PR, $n = 7$).

Tumor response to ripretinib in patients with metastatic melanoma varied by KIT mutation status and prior KIT inhibitor therapy. In nine patients with KIT exon 11 mutation, confirmed ORR was 44% (PR, $n = 4$, 3 in mucosal and 1 in acral) and mPFS was 10.2 months (95% CI 0.6 months-not estimable) (Table 2). In 11 patients with KIT exon 17 mutation, confirmed ORR was 18% (CR, $n = 1$ in acral; PR, $n = 1$ in mucosal) and mPFS was 13.6 months (95% CI 1.8 months-not estimable). Of the 17 patients without prior KIT inhibitor therapy, the confirmed ORR was 29% (CR, $n = 1$; PR, $n = 4$) with an mPFS of 10.2 months (95% CI 1.8 months-not estimable). Of the nine patients with prior KIT inhibitor therapy, confirmed ORR was 11% (PR, $n = 1$) with an mPFS of 2.9 months (95% CI 0.6 month-not estimable) (Figure 1C).

Among the four patients who dose-escalated to ripretinib 150 mg BID after disease progression on 150 mg QD, the median PFS1 (mPFS1) was 6.9 months (95% CI 1.7 months-not estimable) and median PFS2 (mPFS2) was 4.9 months (95% CI 0.8 month-not estimable). The ratio of mPFS2/mPFS1 was 71%. Of note, ripretinib was the second-line therapy in one patient, third-line therapy in two patients, and sixth-line therapy in one patient for the four patients who dose-escalated.

Safety

Ripretinib was well tolerated among patients with KIT-altered metastatic melanoma. The most common treatment-related treatment-emergent adverse events (TEAEs) of any grade in ≥15% of patients treated with ripretinib 150 mg QD (including 150 mg BID period) were increased lipase, alopecia, actinic keratosis, myalgia, arthralgia, decreased appetite, fatigue, hyperkeratosis, nausea, and palmar-plantar erythrodysesthesia syndrome (Table 4). Lipase increase was the only treatment-related

grade 3 TEAE occurring in >5% of patients. There were no grade 4-5 treatment-related TEAEs. Two patients had seven serious TEAEs that were possibly treatment-related (one patient had grade 3 diastolic dysfunction, and another had grade 3 worsening colitis, grade 2 abdominal pain, grade 1 pyrexia, grade 1 alkaline phosphatase increase, grade 2 blood bilirubin increase, and grade 3 duodenal perforation).

A summary of dose modifications among patients with KIT-altered metastatic melanoma receiving ripretinib are presented in Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100520. Any dose increase, interruption, or reduction in patients receiving ripretinib occurred in 4 (15%), 17 (65%), and 5 (19%) patients, respectively. The four patients with dose increase were those who dose-escalated to ripretinib 150 mg BID after disease progression on 150 mg QD. Five (19.2%) patients had TEAEs leading to treatment discontinuation; two had TEAEs that were not treatment-related, and three patients each reported one of the following events: grade 2 anemia (possibly treatment-related), grade 3 duodenal perforation (possibly treatment-related), and grade 3 heartburn (probably treatment-related).

DISCUSSION

Results of the present analysis in patients with KIT-altered metastatic melanoma enrolled in the expansion phase of the ripretinib phase I study showed that ripretinib has clinical efficacy with a confirmed ORR of 23% and mPFS of 7.3 months and an acceptable safety profile. Specifically, KIT inhibitor-naive patients had a greater response (ORR 29%, mPFS 10.2 months) than those who received prior KIT inhibitor therapy (ORR 11%, mPFS 2.9 months).

KIT mutations or amplifications are most common in acral and mucosal melanomas (∼10%-40%).[4-6] KIT mutations in melanoma are observed in exons 9, 11, 13, 17, and 18, with considerable overlap in GIST.[4,9,26] Given the established safety and efficacy of ripretinib in patients with advanced GIST, the efficacy and safety of ripretinib were assessed in patients with KIT-altered metastatic melanoma. Compared to KIT-mutant GIST, previous studies of KIT inhibition in melanoma have demonstrated modest activity, with mPFS of 3-6 months, ORR of 16%-30%, and nearly all responses observed in melanoma harboring a KIT mutation in exon 11 or exon 13.[22,23] The mechanisms of intrinsic and adaptive resistance to ripretinib in melanoma are not fully understood. Melanomas exhibit a relatively higher degree of plasticity when compared with GISTs, which can allow melanoma cells to engage in a wider array of adaptive responses.[27,28] Ripretinib has the broadest and most potent pre-clinical inhibitory profile of all KIT inhibitors that are currently approved for GIST.[18] If melanoma resistance to KIT inhibition is mediated through secondary resistance mutations, ripretinib should have the highest chance to suppress or overcome such resistance. It is worth noting that ripretinib does have some inhibitory activity in downstream signaling intermediates of KIT kinase activity.[18] Future
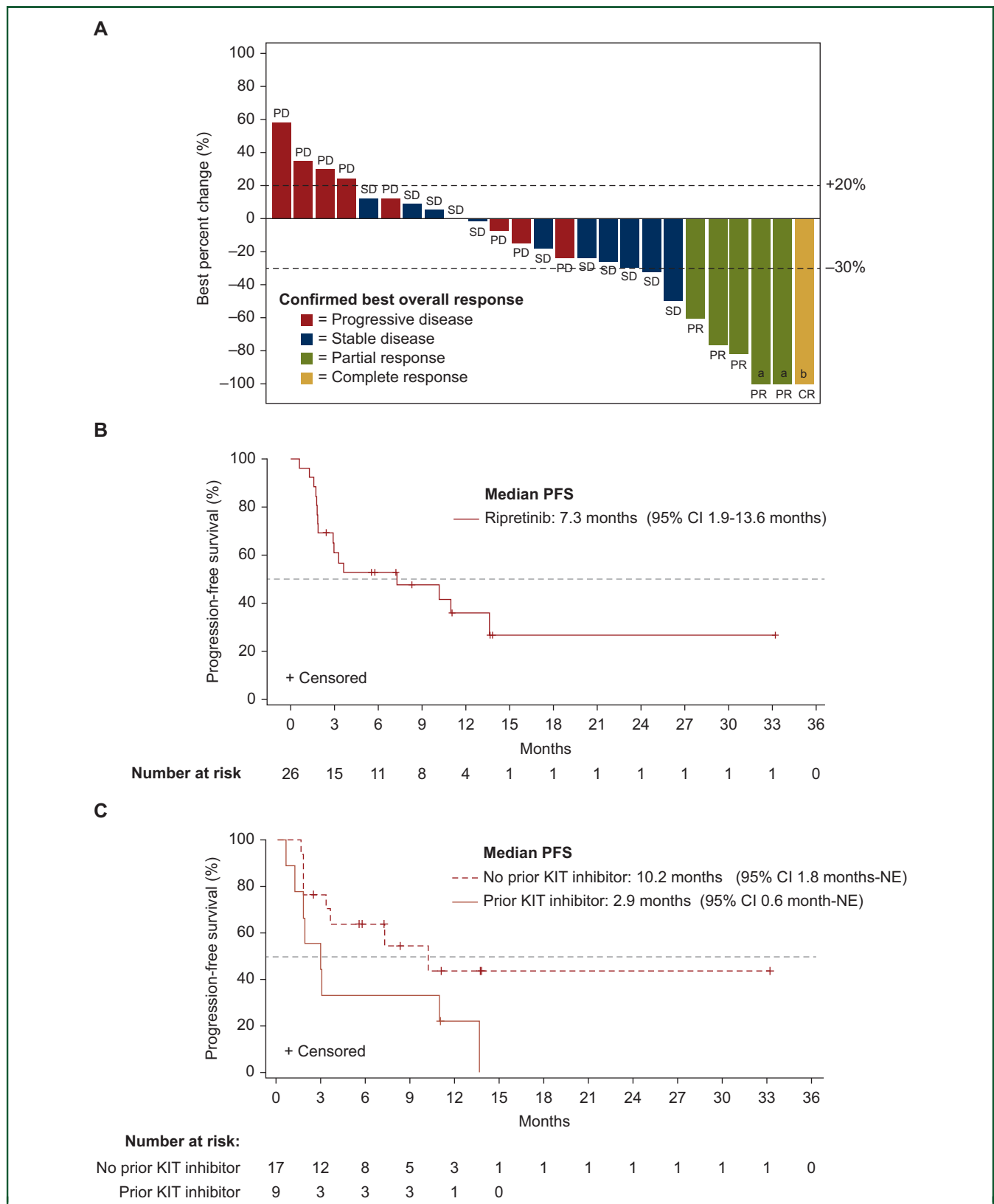
Figure 1. Tumor response and progression-free survival following ripretinib treatment.
(A) Best percentage change from the baseline sum of diameters in target lesions and confirmed best overall response to ripretinib. (B) Kaplan–Meier curve of PFS. (C) Kaplan–Meier curve of PFS based on prior KIT inhibitor therapy.
CI, confidence interval; CR, complete response; EDC, electronic data capture; NE, not estimable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a]CR in target lesion and SD in non-target lesion, overall PR.
[b]The best percentage decrease of 68.9% in the target lymph node lesion per EDC was corrected to 100%, accounting for a normalized lymph node with a perpendicular axis <10 mm.

Table 2. Efficacy of ripretinib, overall and by *KIT*-alteration status, in patients with metastatic melanoma[a]

	Total (n = 26)	Exon 11 (n = 9)	Exon 17 (n = 11)	Other[b] (n = 6)
Best overall response, n (%)				
Confirmed CR	1 (4)	0	1 (9)	0
Confirmed PR[c]	5 (19)	4 (44)	1 (9)	0
SD (≥6 weeks)	11 (42)	3 (33)	5 (46)	3 (50)
PD	8 (31)	1 (11)	4 (36)	3 (50)
No follow-up radiological assessment	1 (4)	1 (11)	0	0
Confirmed ORR[c,d] % (95% CI)	23 (9-44)	44 (14-79)	18 (2-52)	0
Median duration of confirmed response[e] (range), months	9.1 (6.9-31.3)	10.5 (8.3-31.3)	8.1 (6.9-9.2)	N/A
Median time to confirmed response (range), months	1.9 (1.4-2.0)	1.9 (1.8-2.0)	1.7 (1.4-1.9)	N/A
Median PFS, (95% CI), months	7.3 (1.9-13.6)	10.2 (0.6-NE)	13.6 (1.8-NE)	—[f]

CI, confidence interval; CR, complete response; N/A, not applicable; NE, not estimable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a]Tumor biopsy at screening or archival tumor sample allowed if no anticancer therapy was administered since sample collection.
[b]*KIT* mutation in exon 13 (n = 4), exon 18 (n = 1), and *KIT*-amplification (n = 1).
[c]In addition, there were two unconfirmed PRs resulting in an ORR of 31% (95% CI 14%-52%).
[d]Among 25 patients with a follow-up imaging assessment, ORR was 32% (8/25; CR, n = 1; PR, n = 7). A 53-year-old female who had received four prior lines of systemic melanoma therapy before enrolling in this study did not have follow-up assessment due to early death. Her medical course was complicated by gastric hemorrhage, and she stopped ripretinib on cycle 1 day 15 due to respiratory failure secondary to pneumonia that resulted in her death, and both events were unrelated to ripretinib treatment.
[e]Including the two unconfirmed PRs, the median duration of response was 8.7 months (range, 1.7-31.3 months).
[f]The median PFS was not included due to limited number of patients with *KIT* exon 13, exon 18 mutations, and *KIT*-amplification.

exploratory studies using tumor tissue and longitudinal circulating tumor DNA analysis would be beneficial for elucidating the mechanisms that could potentially contribute to drug resistance in melanoma.

The clinical benefit of ripretinib observed in this study confirms and expands the results of previous studies evaluating KIT inhibition as a therapeutic strategy in a selected group of patients with metastatic melanoma and *KIT* alterations. Of note, the proportion of patients who received prior therapy in this study (88% had immunotherapy and 35% had KIT inhibitor) was much higher than in previous studies. While cross-study comparisons cannot readily be made, it appears that despite the heavy pre-treatment, the clinical benefit in mPFS (7.3 months) and duration of response (9.1 months) with ripretinib in *KIT*-altered metastatic melanoma compare favorably to those reported previously for other KIT inhibitors.[22,23] Also, the mPFS with ripretinib in KIT inhibitor-naive patients compared favorably to previously reported data.[22,23] Thus, it is plausible that early treatment with a broad-spectrum KIT inhibitor such as ripretinib in patients with *KIT*-altered metastatic melanoma could effectively suppress the emergence of adaptive resistance mutations.

Immune checkpoint inhibitors (ICIs) such as anti-programmed cell death protein 1 (PD-1) or anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) have shown activity in acral and mucosal melanomas.[29-31] McKean et al. investigated the effect of CTLA-4 inhibition in 35 patients with *KIT*-mutant metastatic melanoma and reported an ORR of 20% and mPFS of 3 months.[23] Among the 20 patients with *KIT*-mutant melanoma treated with a PD-1 inhibitor, ORR was 35% and mPFS was 3.2 months. Interestingly, three of the seven patients with *KIT* exon 17 mutant melanoma, many of whom appear to have minimal or no sensitivity to currently available KIT inhibitors,[24] had a PR to PD-1 inhibition. We observed a marked tumor response to

Table 3. Treatment response to ripretinib by *KIT*-alteration status in patients with metastatic melanoma

Patient	*KIT*-alteration[a]	Best percentage change in target lesions from baseline[b]	Confirmed best overall response[b]
1[c]	Exon 11 D579G, V560D, Exon 17 D816N	−60.0	PR
2	Exon 11 L576P	−100.0	PR[d]
3	Exon 11 L576P	−81.8	PR
4	Exon 11 L576P	−100.0	PR[d]
5	Exon 11 L576P	−17.9	SD
6	Exon 11 V559A	No data on response	No data on response
7	Exon 11 V560D	+8.7	SD
8	Exon 11 V560E	+24.2	PD
9	Exon 11 W557R	−49.6	SD
10	Exon 17 D816H	−29.6	SD
11	Exon 17 D816V	+58.5	PD
12	Exon 17 D820V	+5.0	SD
13	Exon 17 D820Y	−68.9	CR[e]
14	Exon 17 I798V	−1.2	SD
15	Exon 17 N822K	−25.8	SD
16	Exon 17 N822K	−32.6	SD
17	Exon 17 N822Y	−6.8	PD
18	Exon 17 N822Y	−23.8	PD
19	Exon 17 N822Y	+29.8	PD
20	Exon 17 Y823D	−76.4	PR
21	Exon 13 K642E	+12.0	PD
22	Exon 13 K642E	−24.4	SD
23	Exon 13 R634Q	+34.7	PD
24	Exon 13 V654A	0.0	SD
25	Exon 18 A829P	−14.8	PD
26	Whole gene (4q12) amplification	+12.5	SD

CR, complete response; PD, progressive disease; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a]Tumor biopsy at screening or archival tumor sample allowed if no anticancer therapy was administered since sample collection.
[b]Assessed in the ripretinib 150-mg QD period.
[c]Patient included in the exon 11 group for efficacy assessment.
[d]CR in target lesion and SD in non-target lesion, overall PR.
[e]Lymph node target lesions can achieve CR without 100% reduction in target lesions, as RECIST v1.1 only requires reduction of the target lymph node lesion to within the normal range with a perpendicular axis <10 mm.

Table 4. Treatment-related treatment-emergent adverse events reported in ≥15% of patients with *KIT*-altered metastatic melanoma receiving ripretinib

Preferred term, n (%)	All grades (n = 26)	Grade 1 (n = 26)	Grade 2 (n = 26)	Grade 3[a] (n = 26)
Any event	22 (85)	4 (15)	8 (31)	10 (39)
Lipase increased	13 (50)	2 (8)	3 (12)	8 (31)
Alopecia	9 (35)	4 (15)	5 (19)	N/A[b]
Actinic keratosis	5 (19)	4 (15)	1 (4)	0
Myalgia	5 (19)	5 (19)	0	0
Arthralgia	4 (15)	2 (8)	2 (8)	0
Decreased appetite	4 (15)	3 (12)	1 (4)	0
Fatigue	4 (15)	3 (12)	1 (4)	0
Hyperkeratosis	4 (15)	3 (12)	1 (4)	0
Nausea	4 (15)	3 (12)	1 (4)	0
Palmar-plantar erythrodysesthesia syndrome	4 (15)	3 (12)	1 (4)	0

N/A, not applicable.
[a]There were no grade 4-5 treatment-related treatment-emergent adverse events.
[b]As per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, alopecia is only assessed as grade 1 or 2.

ripretinib in patients with metastatic melanoma previously treated with ICI and *KIT* mutations in exon 11 or exon 17, indicating ripretinib may be a viable treatment option for ICI-refractory metastatic melanoma. The small number of patients with other *KIT* alterations (mutations in exon 13, exon 18, and *KIT*-amplification) in this study limits our interpretation of the specific effect of ripretinib on these *KIT* alterations in melanoma. Nonetheless, the broad-spectrum inhibition of *KIT/PDGFRA* mutations by ripretinib in patients with advanced GIST and pre-clinical cell lines relevant in GIST, systemic mastocytosis, leukemia, and lung cancer suggests a similar inhibitory profile of ripretinib in *KIT*-mutant melanoma.[18,32]

A total of four patients with *KIT*-altered metastatic melanoma underwent ripretinib dose escalation to 150 mg BID after disease progression on 150 mg QD. The decision to initiate ripretinib dose escalation was at the discretion of the investigator, based on the patient's best interest. Interestingly, a trend toward additional clinical benefit was observed with ripretinib dose escalation to 150 mg BID in patients with *KIT*-altered metastatic melanoma, consistent with recent studies employing a similar strategy in patients with advanced GIST.[33,34]

Ripretinib had an acceptable safety profile in *KIT*-altered metastatic melanoma. Consistent with the safety profile observed in ≥fourth-line advanced GIST in the pivotal study, lipase increase was the only treatment-related grade 3 TEAE occurring in >5% of patients.[17] Enzyme elevations have been reported with other KIT inhibitors, such as nilotinib, in metastatic melanoma harboring *KIT* alterations.[35] There were no grade 4-5 treatment-related TEAEs in this study. This safety data include the four patients who had ripretinib dose escalation to 150 mg BID after progression on 150 mg QD, and one among them was continuing treatment at the time of this analysis.

Although consistent with the size of other studies in *KIT*-altered melanoma, the cohort of *KIT*-altered melanoma in this study is limited by the small sample size and single-arm design. The small sample size is to be expected, as *KIT* mutations are only observed in ∼3% of all melanomas.[6-8] Another limitation of the study was that the decision to initiate ripretinib dose escalation to 150 mg BID after

disease progression on ripretinib 150 mg QD was at the discretion of the investigator; however, it was implemented in only four patients. Therefore, the trend toward additional clinical benefit with ripretinib dose escalation, while consistent with studies in GIST, may be limited. Lastly, most patients had mucosal or acral melanoma, potentially limiting the generalizability of these findings to other less common melanoma subtypes harboring *KIT* alterations.

In conclusion, ripretinib demonstrated encouraging efficacy and a manageable safety profile in patients with *KIT*-altered metastatic melanoma, suggesting ripretinib may have a clinically meaningful role in the treatment of these patients. These results provide a rationale for *KIT* mutational testing in patients with mucosal, acral, or CSD melanomas and support ripretinib as a therapeutic option in patients with *KIT*-altered metastatic melanoma after disease progression on ICI therapy.

ROLE OF THE FUNDER

This study was designed by Deciphera Pharmaceuticals, LLC, with input from the investigators. Deciphera Pharmaceuticals, LLC, analyzed the data collected by the investigators and interpreted jointly with all the authors. The authors had access to the data to verify the completeness and accuracy of the data reported and for the adherence of the study to the protocol. The corresponding author had full access to all data in this study and had final responsibility for the decision to submit for publication.

DISCLOSURE

DATA SHARING

Qualified scientific and medical researchers can make requests for individual participant data that underlie the results reported in this article, after de-identification, at info@deciphera.com. Proposals for data will be evaluated and approved by Deciphera at its sole discretion. All approved researchers must sign a data access agreement before accessing the data. Data will be available as soon as possible but no later than 1 year of the acceptance of the article for publication, and for 3 years after article publication. Deciphera will not share data from identified participants or a data dictionary.

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