# Phase 1 study of ripretinib, a broad-spectrum KIT and PDGFRA inhibitor, in patients with *KIT*-mutated or *KIT*-amplified melanoma

F. Janku[1], S. Bauer[2], K. Shoumariyeh[3], R.L. Jones[4], A. Spreafico[5], J. Jennings[6], C. Psoinos[6], J. Meade[6], R. Ruiz-Soto[6], P. Chi[7]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Medical Oncology, University Hospital Essen Westdeutsches Tumorzentrum, Essen, Germany; [3]Department of Medicine I, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany and German Cancer Consortium (DKTK), Partner Site Freiburg and German Cancer Research Center (DKFZ), 69120 Heidelberg, Germany, [4]Medical Oncology, Royal Marsden Hospital NHS Foundation Trust, London, UK, [5]Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, and Department of Medicine, University of Toronto, Toronto, ON, Canada, [6]Deciphera Pharmaceuticals, LLC, Waltham, MA, USA, [7]Human Oncology and Pathogenesis Program/Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

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## INTRODUCTION

- *KIT* alterations (mutations or amplifications) are observed in 3% of all melanomas and are most common in melanomas arising in mucosal (about 30%), acral (20%), and chronically sun-damaged skin (20%)[1,2]
- Previous studies have assessed the efficacy of KIT inhibitors such as imatinib, sunitinib, dasatinib, and nilotinib in patients with *KIT*-altered metastatic melanoma with objective response rate (ORR) ranging between 16%–30% and median progression free-survival (PFS) of 3–6 months[3,4]
- There are no approved KIT inhibitors for *KIT*-altered metastatic melanoma and clinical practice guideline recommends specified KIT inhibitors as second-line therapy in certain situations[5]
- Ripretinib, a switch-control tyrosine kinase inhibitor of KIT and PDGFRA, is approved for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) as ≥fourth-line therapy in the US, Canada, Australia, Hong Kong, and China[6-9]
- We report the efficacy and safety of a starting dose of ripretinib 150 mg once daily (QD) in 26 patients with *KIT*-altered metastatic melanoma enrolled in the expansion phase of ripretinib phase 1 study (NCT102571036)

## METHODS

- Twenty-six patients with *KIT*-altered metastatic melanoma were treated with ripretinib at the recommended phase 2 dose of 150 mg QD in repeated 28-day cycles in the expansion phase of the ripretinib phase 1 study
- Tumour progression was assessed by the investigator using computed tomography/magnetic resonance imaging according to Response Evaluation Criteria In Solid Tumours (RECIST) Version 1.1 on Day 1 of Cycles 3, 5, 7, and every 3 cycles thereafter, and a final study visit
- Responses were confirmed with follow-up imaging at least 28 days later. ORR was defined as the proportion of patients with a complete response (CR) plus partial response (PR)
- 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
- Efficacy was evaluated in patients receiving ripretinib 150 mg QD; safety analyses were performed in all patients receiving a ripretinib dose (includes 150 mg QD and 150 mg BID periods)
- Adverse events (AEs) were graded by the investigators using the NCI Common Terminology Criteria for Adverse Events version 4.03

## RESULTS

### Table 1. Patient disposition

| Disposition, n (%) | Ripretinib (n = 26) |
|---|---|
| **Ongoing** | 9 (35) |
| **Discontinued treatment** | 17 (65) |
| Adverse event | 5 (19) |
| Progressive disease | 10 (39) |
| Other[a] | 2 (8) |

[a]Both patients discontinued due to clinical progression.

Post-primary follow-up analysis
Data cutoff
**May 10, 2021**

**ClinicalTrials.gov: NCT102571036**

### Table 2. Baseline characteristics in patients with *KIT*-altered metastatic melanoma receiving ripretinib

| Characteristics | Ripretinib (n = 26) |
|---|---|
| **Age, median (range), years** | 66 (32, 86) |
| <65 | 12 (46) |
| ≥65 | 14 (54) |
| **Sex, n (%)** | |
| Male | 12 (46) |
| Female | 14 (54) |
| **ECOG Performance Status** | |
| 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) |

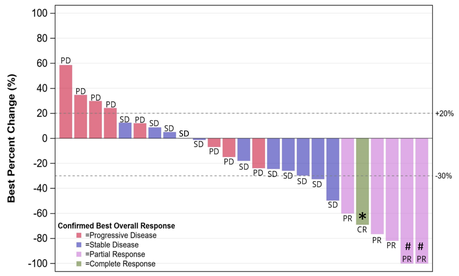
| Characteristics | Ripretinib (n = 26) |
|---|---|
| **Prior anticancer therapy, n (%)** | |
| No. of prior lines of therapy[a], median | 2 |
| 0 | 3 (12) |
| 1 | 5 (19) |
| 2 | 8 (31) |
| 3+ | 10 (38) |
| Immunotherapy | 23 (89) |
| KIT inhibitor[b,c] | 9 (35) |
| **KIT mutation status[d], n (%)** | |
| Exon 11 | 9 (35) |
| Exon 13 | 4 (15) |
| Exon 17 | 11 (42) |
| Exon 18 | 1 (4) |
| Amplification | 1 (4) |

[a]Prior combination therapies were counted as 1-prior line of therapy. [b]Patients received ≥1 KIT inhibitor: imatinib, imatinib plus ipilimumab, imatinib plus pembrolizumab, nilotinib, axitinib, and dasatinib plus crizotinib. [c]Overall, 8 patients received imatinib either as a single agent or combination therapy. [d]Biopsy at screening or archival tumour sample allowed if no anticancer therapy was administered since sample collection. ECOG, Eastern Cooperative Oncology Group.

## *Efficacy*

- Among 26 patients, confirmed ORR was 23% (95% confidence interval [CI] 9.0, 43.6; *KIT* exon 11: 4 PR, 3 in mucosal and 1 in acral; *KIT* exon 17: 1 CR in acral and 1 PR in mucosal; **Figure 1**). The confirmed and unconfirmed ORR was 31% (**Table 3**)
- Among 26 patients, the median PFS was 7.3 months (95% CI 1.9, 13.6; **Figure 2**) and median duration of response was 9.1 months (range 6.9–31.3, **Table 3**)
- Among 25 patients with follow-up imaging assessments, confirmed and unconfirmed ORR was 32% (**Figure 1, Table 3**).
  - A 53-year-old female who received 4 prior lines of systemic melanoma therapy before enrolling did not have a follow-up assessment due to early death. Her medical course was complicated by gastric haemorrhage, and she stopped ripretinib on Cycle 1 Day 15 due to respiratory failure secondary to pneumonia that resulted in death; both events were unrelated to ripretinib treatment
- Tumour response to ripretinib varied by exposure to prior KIT inhibitor therapy (**Figure 3**)
  - Of the 17 patients without prior KIT inhibitor therapy, confirmed ORR was 29.4% (1 CR, 4 PR) with a median PFS of 10.2 months (95% CI 1.8, NE [not estimable])
  - Of the 9 patients with prior KIT inhibitor therapy, confirmed ORR was 11.1% (1 PR) with a median PFS of 2.9 months (95% CI 0.6, NE)
- Ripretinib was dose escalated to 150 mg BID after progressive disease on 150 mg QD in 4 (15%) patients (**Figure 4**). At data cutoff, 9 (35%) patients remained on study treatment (8 on ripretinib 150 mg QD and 1 on ripretinib 150 mg BID)

### Figure 1. Best percent change from baseline in tumour size



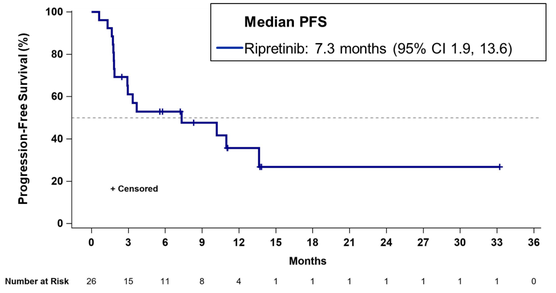

*Lymph node target lesions can achieve CR without 100% reduction in target lesions as RECIST v1.1 only requires reduction of the target lymph node lesion to within the normal range with a perpendicular axis <10mm.
[a]CR in target lesion and SD in non-target lesion, overall PR.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

### Table 3. Efficacy of ripretinib in patients with *KIT*-altered metastatic melanoma

| | Ripretinib (n = 26) |
|---|---|
| **Confirmed CR** | 1 (4) |
| **Confirmed PR[a]** | 5 (19) |
| **SD (≥6 weeks)** | 11 (42) |
| **PD** | 8 (31) |
| **No follow-up radiological assessment** | 1 (4) |
| **Confirmed ORR[a], % (95% CI)** | 23 (9, 44) |
| **Median duration of confirmed response[b] (range), months** | 9.1 (6.9–31.3) |
| **Median PFS (95% CI), months** | 7.3 (1.9, 13.6) |

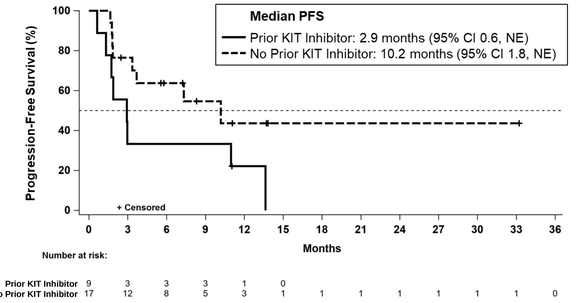
[a]In addition, there were 2 unconfirmed PRs resulting in an ORR of 31% (95% CI, 14.3, 51.8). [b]Including the 2 unconfirmed PRs, the median duration of response was 8.7 months (range 1.7–31.3).
CI, confidence interval; CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; PFS, progression-free survival; SD, stable disease.

### Figure 2. Kaplan-Meier plot of PFS in patients with *KIT*-altered metastatic melanoma



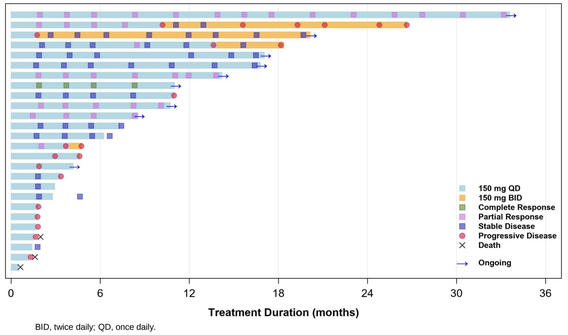

CI, confidence interval; PFS, progression-free survival.

### Figure 3. Kaplan-Meier plot of PFS by prior KIT inhibitor therapy




CI, confidence interval; NE, not estimable; PFS, progression-free survival.

### Figure 4. Duration of ripretinib treatment and responses in patients with *KIT*-altered metastatic melanoma




BID, twice daily; QD, once daily.

## *Safety*

- Lipase increased was the only treatment-related Grade 3 treatment-emergent adverse event (TEAE) occurring in >5% of patients (**Table 4**)
- There were no Grade 4–5 TEAEs related to treatment
- Two patients had 7 serious TEAEs that were possibly treatment-related (1 patient had diastolic dysfunction; another had worsening colitis, abdominal pain, pyrexia, alkaline phosphatase increase, blood bilirubin increase, and duodenal perforation)
- Any dose modification in patients receiving ripretinib occurred in 17 (65%) patients, and any TEAE leading to treatment discontinuation occurred in 5 (19%) patients (**Table 5**)

### Table 4. Treatment-related TEAEs in ≥15% of patients with *KIT*-altered metastatic melanoma

| Preferred term, n (%) | All grades | Grade 1 | Grade 2 | Grade 3[a] |
|---|---|---|---|---|
| **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 |
| 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 |
| PPES | 4 (15) | 3 (12) | 1 (4) | 0 |

[a]There were no Grade 4–5 TEAEs related to treatment.
N/A, not applicable; PPES, palmar-plantar erythrodysesthaesia syndrome; TEAE, treatment-emergent adverse event.

### Table 5. Dose modifications in patients with *KIT*-altered metastatic melanoma

| Preferred term, n (%) | Ripretinib (n = 26) |
|---|---|
| **Any dose modification** | 17 (65) |
| Any dose increase | 4 (15) |
| Any dose reduction | 5 (19) |
| Any dose interruption | 17 (65) |
| **Any TEAE leading to treatment discontinuation** | 5 (19)[a] |

[a]Two patients had TEAEs that were not treatment-related, and 3 patients each reported one of the following events: Grade 2 anaemia (possibly treatment-related), Grade 3 duodenal perforation (possibly treatment-related), and Grade 3 heartburn (probably treatment-related). TEAE, treatment-emergent adverse event.

## CONCLUSIONS

- Based on this analysis, ripretinib demonstrated encouraging efficacy in patients with *KIT*-altered metastatic melanoma with a confirmed ORR of 23%, median PFS of 7.3 months, and median duration of response of 9.1 months
- Patients without prior KIT inhibitor therapy had a greater response (ORR 29%, median PFS 10.2 months) than those who had received prior KIT inhibitor therapy (ORR 11%, median PFS 2.9 months)
- Ripretinib had an acceptable safety profile in *KIT*-altered metastatic melanoma consistent with the approved indication in GIST
- The results suggest ripretinib may have a meaningful clinical role in treating patients with *KIT*-altered metastatic melanoma

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**Corresponding Author/Disclosures**

Filip Janku: fjanku@me.com

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