Dermatopathological review of cutaneous squamous cell carcinoma events in patients with gastrointestinal stromal tumor treated with ripretinib

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INTRODUCTION

- Ripretinib, a broad-spectrum KIT and PDGFRA switch-control tyrosine kinase inhibitor, is indicated for patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors, including imatinib[1]
- Ripretinib is a weak inhibitor of BRAF and CRAF in cellular assays[1,2]
- The incidence of all-grade cutaneous squamous cell carcinoma (cuSCC) with the BRAF inhibitors vemurafenib and dabrafenib was 12.5% in a meta-analysis of 6,445 patients from 21 studies[3]
- cuSCC occurred in 7% of 351 patients enrolled in either the phase 1 (NCT02571036) or phase 3 INVICTUS study (NCT03353753) receiving at least 1 dose of ripretinib.[1] Dermatologic evaluation is recommended for suspicious skin lesions that develop during ripretinib treatment
- We present the results of a centralized dermatopathological review of reported cuSCC events with available biopsies that occurred in patients treated with ripretinib

METHODS

- Dermatopathological central review of available biopsy samples of confirmed cuSCC lesions in patients treated with ripretinib in the phase 1 or phase 3 INVICTUS study was performed to characterize the histopathological features, assess any correlation with clinical history, and identify management strategies

Table 1. Clinical studies in this analysis

Study No.	Study design, N[a]	Patient population	Drug dosing	Age (years), median (range)	Dermatologic examination
NCT02571036	A multicenter, phase 1, open-label study of ripretinib to assess safety, tolerability, and efficacy in patients with advanced malignancies (N = 258)	GIST (n = 184) Other solid tumors (n = 74)	28-day cycles Escalation Phase 20, 30, 50, 100, 150, and 200 mg BID; and 100, 150, and 250 mg QD Intrapatient dose escalation was permitted Expansion Phase 150 mg QD Intrapatient dose escalation to ripretinib 150 mg BID was permitted after progression of disease	61 (19–92)	All patients assessed by a dermatologist at baseline, Cycle 5 Day 1, final study visit, and as clinically indicated[b]
NCT03353753 (INVICTUS)	A phase 3, randomized, double-blind, placebo-controlled study in patients with advanced GIST (N = 129)	Ripretinib (n = 85) vs placebo (n = 44)	28-day cycles Ripretinib 150 mg QD Intrapatient dose escalation to ripretinib 150 mg BID was permitted after progression of disease Crossover from placebo to ripretinib arm was permitted after progression of disease	Ripretinib: 59 (29–82) Placebo: 65 (33–83)	All patients assessed by a dermatologist at baseline, Cycle 3 Day 1 and every third cycle thereafter, end-of-treatment visit, and as clinically indicated

[a]Number of patients as of the August 31, 2019 data cutoff for NCT02571036 study and as of the May 31, 2019 cutoff for NCT03353753.
[b]Prior to protocol amendment 3, skin assessments were performed by the investigator during study visits as part of the physical exam.
BID, twice daily; GIST, gastrointestinal stromal tumor; N, number of patients; QD, once daily.

RESULTS

Table 2. Analysis of available cuSCC biopsy samples

Fifteen cuSCC biopsy samples from 10 patients treated with ripretinib at 5 institutions

Phase 1:
14 cuSCC biopsy samples from 9 patients including 8 with GIST
- 13 cuSCC biopsy samples from patients at a starting dose of ripretinib 150 mg QD
- 1 cuSCC biopsy sample from patients at a starting dose of ripretinib 200 mg BID

Phase 3 INVICTUS:
1 cuSCC biopsy sample from a patient with GIST randomized to ripretinib 150 mg QD

BID, twice daily; cuSCC, cutaneous squamous cell carcinoma; GIST, gastrointestinal stromal tumor; QD, once daily.

Table 3. Patient characteristics

Patient	Sex	Age at biopsy (years)	Disease	Site	Time from first dose of ripretinib to biopsy (months)	History of cutaneous malignancy
1	F	58	GIST	Lower extremity	21.7	No
2	F	68	GIST	Head/neck	11.9	No
3	F	61	GIST	Lower extremity	22.8	No
4	M	77	GIST	Shoulder/back/trunk	4.5	Yes
5	M	79	GIST	Shoulder/back/trunk	5.4	No
6	F	76	Melanoma	Lower extremity	3.3	No
	F	76		Lower extremity	–	No
	F	76		Lower extremity	4.8	No
	F	76		Lower extremity	9.5	No
7	F	69	GIST	Head/neck	4.6	No
	F	70		Upper extremity	3.9	No
	F	70		Shoulder/back/trunk	–	No
8	M	78	GIST	Upper extremity	6.8	No
9	M	62	GIST	Head/neck	5.3	No
10	F	79	GIST	Head/neck	–	Yes

– represents unknown. GIST, gastrointestinal stromal tumor.

- Of the 10 patients, 9 were of non-Hispanic ethnicity, 1 not reported
- Median age at cuSCC onset was 76 years (range 58-79 years) and median time from first dose of ripretinib to biopsy was 5.4 months (range 3.3–22.8 months)
- All patients had cuSCC lesions on sun-exposed areas

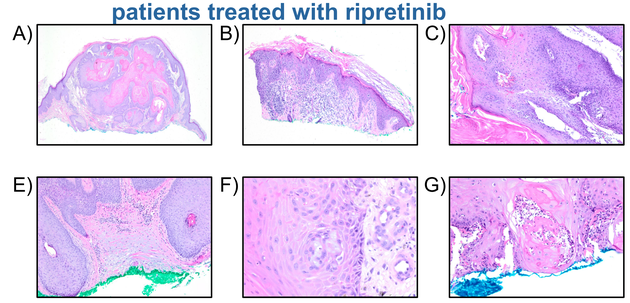
Table 4. cuSCC characteristics

	cuSCC type			Inflammation					
Patient	Invasive and well differentiated	In situ	Tumor thickness (mm)	Tumoral	Stromal	Solar elastosis	Entrapped solar elastosis	Dermal invasion	Micro-abscesses
1	Yes	No	≥2.1	++	++	++	Yes	Yes	Yes
2	Yes	No	≥0.5	+	+	+	No	Yes	No
3	Yes	No	≥2.3	+	++	++	Yes	Yes	No
4	Yes	No	≥3.0	+	++	+	Yes	Yes	Yes
5	Yes	No	≥2.5	++	++	+	No	Yes	Yes
6	N/A	Yes	0.25	+	++	+	No	No	No
	Yes	No	1.0	-	++	+	Yes	Yes	No
	Yes	No	≥0.7	-	+	+	No	Yes	No
	Yes	No	1.5	-	+	++	Yes	Yes	No
7	Yes	No	≥0.8	++	++	++	Yes	Yes	Yes
	Yes	No	1.6	++	++	++	Yes	Yes	Yes
	Yes	No	1.7	+	++	+++	Yes	Yes	Yes
8	Yes	No	3.2	+	+++	++	Yes	Yes	Yes
9	Yes	No	2.1	+	++	+++	No	Yes	Yes
10	Yes	No	1.8	++	+++	+++	Yes	Yes	Yes

N/A, not available; cuSCC, cutaneous squamous cell carcinoma.

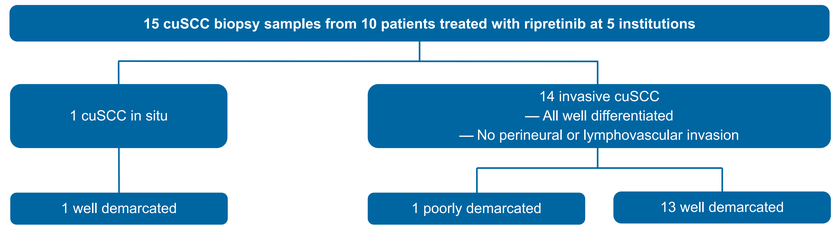
- All patients displayed low-risk cuSCC characteristics such as well-differentiated tumor, ≤6 mm in thickness, and no perineural or lymphovascular invasion

Figure 1. Representative histologic images of cuSCC characteristics in patients treated with ripretinib



A) Invasive and well-differentiated cuSCC
B) In situ cuSCC
C) Intratumoral inflammation
D) Stromal inflammation
E) Solar elastosis
F) Entrapped solar elastosis
G) Neutrophilic microabscesses

Figure 2. Summary of dermatopathological analysis



cuSCC, cutaneous squamous cell carcinoma.

- Dermatopathological analysis indicated low-risk cuSCC lesions, a well-demarcated cuSCC in situ lesion in 1 sample and invasive cuSCC in 14 samples. All 14 invasive cuSCC lesions were well differentiated with 13 well demarcated and 1 poorly demarcated
- Treatment options for low-risk cuSCC lesions include curettage and electrodessication, cryotherapy, and surgical excision (including standard outpatient Mohs micrographic surgery if necessary)

CONCLUSIONS

- Based on the samples analyzed, patients who developed cuSCC lesions while on ripretinib therapy were elderly with median age of 76 years
- The cuSCC lesions occurred in sun-exposed areas, did not show aggressive histopathological features, and were analogous to their lowest-risk ultraviolet-induced counterparts
- Based on this analysis, the low-risk cuSCC lesions in patients treated with ripretinib can generally be managed using local interventions without the need for dosing modifications or interruptions

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