Updated results of phase 1 study of ripretinib (DCC-2618), a broad-spectrum KIT and PDGFRA inhibitor, in patients with gastrointestinal stromal tumor (GIST) by line of therapy (NCT02571036)

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Abstract: C077

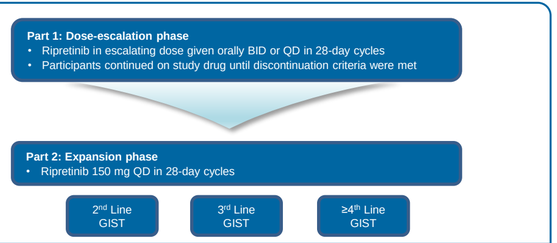
INTRODUCTION

- Gastrointestinal stromal tumors (GISTs) are the most common soft tissue sarcoma of the gastrointestinal (GI) tract[1]
- The vast majority (~85%) of GISTs have oncogenic mutations in either KIT or PDGFRA kinases[2]
- Despite the clinical benefit provided by the tyrosine kinase inhibitors, imatinib, sunitinib, and regorafenib, patients with advanced GIST eventually develop drug-resistance
- An unmet need exists for well-tolerated treatments that (i) broadly inhibit primary and secondary/drug-resistant mutated KIT and PDGFRA kinases and (ii) delay disease progression[3]
- **Ripretinib is a novel, tyrosine kinase switch control inhibitor** that is designed to broadly inhibit oncogenic KIT and PDGFRA signaling through a **unique dual mechanism of action that secures the target kinase into an inactive conformation** resulting in the inhibition of downstream signaling and cell proliferation[3]
  - Ripretinib binds to the switch pocket, preventing access to the switch pocket by the activation loop, thereby locking the kinase into the inactive state
  - Additionally, ripretinib binds to the activation loop, further preventing its access to the switch pocket and blocking kinase activity
- Ripretinib was assessed in a phase 1, open-label, first-in-human, dose-escalation study designed to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary antitumor activity of oral ripretinib in adult patients with advanced malignancies, including advanced GIST (NCT02571036)
- **Updated preliminary** results presented by George *et al*[4] at ESMO 2018 demonstrated encouraging efficacy
  - All doses of ≥100 mg per day were associated with reductions in KIT mutant allele frequency in plasma circulating tumor DNA, including the KIT mutations least sensitive to ripretinib *in vitro*
  - Although daily doses of up to 400 mg were tested, **a maximum tolerated dose was not determined**
- Based on preclinical *in vivo* and *in vitro* pharmacology studies, 150 mg once daily (QD) is predicted to maintain the pharmacokinetic exposure above presumed threshold for efficacy in >90% of patients
  - Safety data collected from the phase 1 dose-escalation phase support administration of **150 mg QD as the recommended starting dose to be used in the expansion phase**
- This presentation reports updated results from the escalation and expansion phases of the phase 1 study for patients who were treated at 150 mg QD as the starting dose
- Based on the clinical activity observed in heavily pretreated patients with GIST in this phase 1 study, ripretinib at 150 mg QD is being evaluated in two phase 3 studies:
  - **INVICTUS (NCT03353753)** in ≥4th line patients with GIST, compared with placebo; results reported at ESMO 2019[5]
  - **Intrigue (NCT03673501)** in 2nd line patients with GIST, compared with sunitinib

METHODS

- The phase 1 study included a dose-escalation phase that tested oral ripretinib QD or twice daily (BID) in 28-day cycles
  - In this phase, ripretinib dose levels assessed were 20, 30, 50, 100, 150, 200 mg BID or 100, 150, 250 QD
  - The subsequent expansion phase tested the recommended dose of ripretinib 150 mg QD in 6 cohorts, including cohorts for patients with GIST based on prior lines of therapy (2nd, 3rd, and ≥4th line)
- Local, investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST 1.1) response assessments were performed every 2 cycles, and patients in the expansion cohorts who progressed per RECIST 1.1 were allowed to dose escalate to 150 mg BID
- Safety and efficacy data are reported from the **August 10, 2019, data cutoff**

Figure 1. Phase 1 dose-escalation (part 1) and expansion (part 2) study design



RESULTS

- Efficacy and safety results from the escalation and expansion phases of the phase 1 study for patients with GIST treated at ripretinib 150 mg QD as the starting dose are presented here
- Demographics and baseline characteristics by line of therapy are shown in **Table 1**
  - 142 patients with GIST in the escalation and expansion phases were treated at 150 mg QD dose
  - Number of patients by line of therapy were as follows: 31 2nd line, 28 3rd line, and 83 ≥4th line patients
  - 135 patients (95.1%) had KIT-mutant GIST, and 7 patients (4.9%) had PDGFRA-mutant GIST

Table 1. Baseline patient characteristics

Characteristics	2nd Line (n=31)	3rd Line (n=28)	≥4th Line (n=83)	Total (n=142)
Age at informed consent, years				
Mean (SD)	59.8 (11.92)	64.0 (8.33)	59.5 (11.91)	60.4 (11.36)
Median	60.0	63.5	59.0	60.0
Min, Max	32, 80	48, 82	27, 87	27, 87
Age category, n (%), years				
18 ≤ Age < 65	18 (58.1)	15 (53.6)	57 (68.7)	90 (63.4)
≥ 65	13 (41.9)	13 (46.4)	26 (31.3)	52 (36.6)
Sex, n (%)				
Male	14 (45.2)	17 (60.7)	52 (62.7)	83 (58.5)
Female	17 (54.8)	11 (39.3)	31 (37.3)	59 (41.5)
Race, n (%)				
American Indian or Alaska Native	0	0	3 (3.6)	3 (2.1)
Asian	2 (6.5)	1 (3.6)	6 (7.2)	9 (6.3)
Black or African American	4 (12.9)	2 (7.1)	7 (8.4)	13 (9.2)
White	25 (80.6)	25 (89.3)	63 (75.9)	113 (79.6)
Other	0	0	4 (4.8)	4 (2.8)
Eastern Cooperative Oncology Group (ECOG) performance status, n (%)				
0	16 (51.6)	13 (46.4)	38 (45.8)	67 (47.2)
1	15 (48.4)	15 (53.6)	42 (50.6)	72 (50.7)
2	0	0	3 (3.6)	3 (2.1)
Primary mutation (determined by molecular pathology report), n (%)				
KIT exon 11	26 (83.9)	19 (67.9)	58 (69.9)	103 (72.5)
KIT exon 9	3 (9.7)	8 (28.6)	15 (18.1)	26 (18.3)
KIT other exons	0	1 (3.6)	5 (6.0)	6 (4.2)
PDGFRA	2 (6.5)	0	5 (6.0)	7 (4.9)
KIT/PDGFRA wild type	0	0	0	0

SD, standard deviation

Efficacy

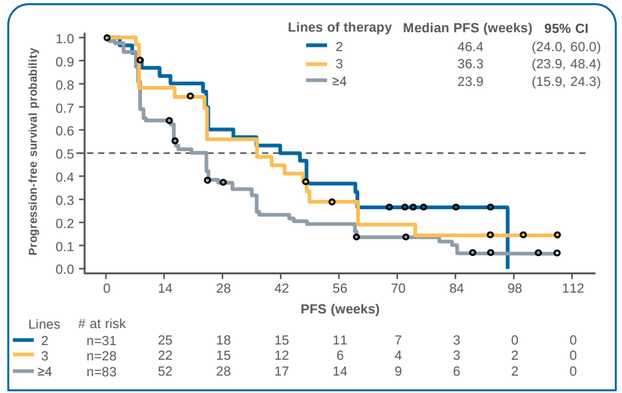
- The confirmed-only complete response (CR), partial response (PR), stable disease, and progressive disease are presented in **Table 2**
  - There were no CRs observed
- The objective response rate (ORR; proportion of patients with CR + PR) is as follows:
  - 2nd line patients: ORR = 19.4%
  - 3rd line patients: ORR = 14.3%
  - ≥4th line patients: ORR = 7.2%
- Median progression-free survival (PFS) per investigator assessment, by line of therapy, is as follows (**Figure 2**):
  - 46.4 weeks in 2nd line patients; 8 patients censored
  - 36.3 weeks in 3rd line patients; 6 patients censored
  - 23.9 weeks in ≥4th line patients; 12 patients censored

Table 2. Efficacy by line of therapy in patients with GIST receiving ripretinib 150 mg QD

Parameters	2nd Line (n=31)	3rd Line (n=28)	≥4th Line (n=83)
Best response (confirmed only), n (%)			
CR	0	0	0
PR	6 (19.4)	4 (14.3)	6 (7.2)
Stable disease	21 (67.7)	18 (64.3)	49 (59.0)
Progressive disease	4 (12.9)	6 (21.4)	22 (26.5)
Not evaluable	0	0	1 (1.2)
No response assessment	0	0	5 (6.0)
ORR, n (95% CI)	19.4 (7.5, 37.5)	14.3 (4.0, 32.7)	7.2 (2.7, 15.1)
Duration of treatment[a]			
Mean, weeks (SD)	56.1 (34.24)	57.5 (32.95)	44.9 (36.58)
Median, weeks	64	51	29
Min, Max	4, 132	8, 124	0.1, 140
Duration of response			
n	6	4	6
Number of events	3	1	3
Median, weeks	80	NE	76.1
95% CI	24.7, 80.0	52.1, NE	24.1, NE
PFS			
Number of censored patients	8	6	12
Median, weeks	46.4	36.3	23.9
95% CI	24.0, 60.0	23.9, 48.4	15.9, 24.3

[a]64 subjects escalated to 150 mg BID among patients with GIST in the 150 mg QD dose group.
CI, confidence interval; CR, complete response; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response; SD, standard deviation.
Local (investigator) response assessment.

Figure 2. Median PFS by line of therapy for patients with GIST treated with ripretinib 150 mg QD



Safety

- The most common all grade treatment emergent adverse events (TEAEs) (in >10% of patients) are shown in **Table 3**
- The most common grade 3 or 4 adverse events (in >5% of patients) were increase in lipase level, 25 (17.6%); anemia, 11 (7.7%); and abdominal pain, 11 (7.7%)

Table 3. All grade TEAEs, regardless of relatedness, in >10% of patients with GIST treated with ripretinib 150 mg QD

Preferred term	Grade 1/2, n (%) (n=142)	Grade 3/4, n (%) (n=142)	All grades, n (%) (n=142)
Alopecia	86 (60.6)	0	86 (60.6)
Fatigue	74 (52.1)	4 (2.8)	78 (54.9)
Myalgia	68 (47.9)	0	68 (47.9)
Nausea	64 (45.1)	2 (1.4)	66 (46.5)
Palmar-plantar erythrodysesthesia syndrome	62 (43.7)	1 (0.7)	63 (44.4)
Constipation	57 (40.1)	0	57 (40.1)
Decreased appetite	46 (32.4)	2 (1.4)	48 (33.8)
Diarrhea	44 (31.0)	3 (2.1)	47 (33.1)
Muscle spasms	42 (29.6)	0	42 (29.6)
Abdominal pain	28 (19.7)	11 (7.7)	39 (27.5)
Lipase increased	14 (9.9)	25 (17.6)	39 (27.5)
Weight decreased	39 (27.5)	0	39 (27.5)
Vomiting	36 (25.4)	1 (0.7)	37 (26.1)
Headache	35 (24.6)	1 (0.7)	36 (25.4)
Arthralgia	32 (22.5)	0	32 (22.5)
Hypertension	25 (17.6)	7 (4.9)	32 (22.5)
Dry skin	31 (21.8)	0	31 (21.8)
Anemia	19 (13.4)	11 (7.7)	30 (21.1)
Back pain	27 (19.0)	2 (1.4)	29 (20.4)
Dyspnea	25 (17.6)	3 (2.1)	28 (19.7)
Cough	25 (17.6)	0	25 (17.6)
Dizziness	25 (17.6)	0	25 (17.6)
Rash	23 (16.2)	0	23 (16.2)
Actinic keratosis	22 (15.5)	0	22 (15.5)
Hypophosphatemia	15 (10.6)	7 (4.9)	22 (15.5)
Seborrheic keratosis	22 (15.5)	0	22 (15.5)
Hypokalemia	15 (10.6)	4 (2.8)	19 (13.4)
Rash maculo-papular	19 (13.4)	0	19 (13.4)
Blood bilirubin increased	14 (9.9)	4 (2.8)	18 (12.7)
Pain in extremity	17 (12.0)	1 (0.7)	18 (12.7)
Insomnia	17 (12.0)	0	17 (12.0)
Pruritus	17 (12.0)	0	17 (12.0)
Blood creatine phosphokinase increased	13 (9.2)	3 (2.1)	16 (11.3)
Melanocytic nevus	16 (11.3)	0	16 (11.3)
Skin papilloma	16 (11.3)	0	16 (11.3)
Stomatitis	16 (11.3)	0	16 (11.3)
Urinary tract infection	14 (9.9)	2 (1.4)	16 (11.3)
Peripheral sensory neuropathy	15 (10.6)	0	15 (10.6)

TEAE, treatment emergent adverse event.

CONCLUSIONS

- Ripretinib showed encouraging clinical benefit at the recommended dose 150 mg QD, as measured by median PFS and ORR, in patients with advanced GIST
- Ripretinib was generally well tolerated in patients with GIST treated in the 2nd line or later
- Data from the phase 1 expansion study in ≥4th line patients supported the phase 3 INVICTUS study and are consistent with the positive INVICTUS results recently reported at ESMO 2019. INVICTUS evaluated ripretinib as ≥4th line therapy in 129 patients with advanced GIST (ripretinib, n=85; placebo, n=44), meeting the primary endpoint showing significant improvement in median PFS compared with placebo (6.3 vs 1 months, respectively; hazard ratio=0.15 [95% CI, 0.09–0.25]; *P*<0.0001)[5]
- The updated data from the phase 1 study presented here demonstrated a median PFS of 46.4 weeks and support the phase 3 study, **intrigue**, comparing ripretinib to sunitinib in 2nd line patients with GIST

Presented at AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 26 to 30, 2019

Acknowledgments
The investigators would like to thank the patients and their families and caregivers, the investigational site staff of this study, and the medical writing assistance of Akriti Kharbanda, PhD, of ETHOS Health Communications in Yardley, Pennsylvania, which was supported financially by Deciphera Pharmaceuticals, LLC, Waltham, Massachusetts, in compliance with international Good Publication Practice guidelines.
This study was sponsored by Deciphera Pharmaceuticals, LLC.

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