original reports abstract

Switch Control Inhibition of KIT and PDGFRA in Patients With Advanced Gastrointestinal Stromal Tumor: A Phase I Study of Ripretinib

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PURPOSE In advanced gastrointestinal stromal tumor (GIST), there is an unmet need for therapies that target both primary and secondary mutations of pathogenic KIT/PDGFRA oncoproteins. Ripretinib is a novel switch-control kinase inhibitor designed to inhibit a wide range of *KIT* and *PDGFRA* mutations.

PATIENTS AND METHODS This first-in-human, to our knowledge, phase I study of ripretinib (ClinicalTrials.gov identifier: NCT02571036) included a dose-escalation phase and subsequent expansion phase at the recommended phase II dose (RP2D). Eligible patients included those with advanced GIST, intolerant to or experienced progression on ≥ 1 line of systemic therapy, and other advanced malignancies. Safety, dose-limiting toxicities (DLTs), maximum-tolerated dose (MTD), and preliminary antitumor activity were evaluated.

RESULTS At data cutoff (August 31, 2019), 258 patients (n = 184 GIST) were enrolled, with 68 patients in the dose-escalation phase. Three DLTs were reported: grade 3 lipase increase (n = 2; 100 mg and 200 mg twice a day) and grade 4 increased creatine phosphokinase (n = 1; 150 mg once daily). MTD was not reached (maximum dose evaluated, 200 mg twice a day); 150 mg once daily was established as the RP2D. The most frequent (> 30%) treatment-emergent adverse events in patients with GIST receiving ripretinib 150 mg once daily (n = 142) were alopecia (n = 88 [62.0%]), fatigue (n = 78 [54.9%]), myalgia (n = 69 [48.6%]), nausea (n = 65 [45.8%]), palmar-plantar erythrodysesthesia (n = 62 [43.7%]), constipation (n = 56 [39.4%]), decreased appetite (n = 48 [33.8%]), and diarrhea (n = 47 [33.1%]). Objective response rate (confirmed) of 11.3% (n = 16/142) ranging from 7.2% (n = 6/83; fourth line or greater) to 19.4% (n = 6/31; second line) and median progression-free survival ranging from 5.5 months (fourth line or greater) to 10.7 months (second line), on the basis of investigator assessment, were observed.

CONCLUSION Ripretinib is a well-tolerated, novel inhibitor of KIT and PDGFRA mutant kinases with promising activity in patients with refractory advanced GIST.

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INTRODUCTION

Activating genomic alterations in *KIT* or *PDGFRA* drive cellular growth in most gastrointestinal stromal tumors (GISTs) and other cancer types, including systemic mastocytosis and some glioblastomas.[1-4] There is no curative therapy for metastatic GIST. First-line treatment with the tyrosine kinase inhibitor (TKI) imatinib has a median progression-free survival (mPFS) of 1.7-2 years.[5-7] Progression is largely due to the development of secondary resistance mutations in the ATP-binding domain or activation loop of *KIT/PDGFRA*.[1,5-13] Secondary mutations can sterically disrupt binding of some TKIs or result in kinase activation.[13] The mPFS with approved second-line (sunitinib) and third-line (regorafenib) therapies is approximately 5.6 months and 4.8 months, respectively—outcomes that likely reflect incomplete inhibition of secondary resistance mutations.[8,9,14-16] Avapritnib is only approved for treatment of GIST with *PDGFRA* exon 18 mutations, which currently account for approximately 6% of the overall GIST population.[13,17,18] Consequently, an unmet medical need exists for treatments effective against a broad range of *KIT/PDGFRA* mutations in advanced GIST, as well as other cancers that have biologically relevant *KIT/PDGFRA* mutations.

Ripretinib (DCC-2618) is a switch-control TKI designed to broadly inhibit KIT and PDGFRA kinase signaling through a dual mechanism of action (MoA).[19] As dual-switch kinases, KIT and PDGFRA contain an inhibitory switch and an activation loop that can occupy the switch pocket and determine an inactive or active kinase conformation, respectively. Ripretinib is designed to precisely and durably bind to both the switch pocket and the activation loop to prevent kinase activation and

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Treatments against a broad range of *KIT/PDGFRA* mutations in advanced gastrointestinal stromal tumor (GIST) are needed. Efficacy for second-line sunitinib and third-line regorafenib are minimal and avapritinib is limited to GIST with *PDGFRA* exon 18 mutations. This study determined the recommended phase II dose (RP2D) and preliminary safety and efficacy of ripretinib, a novel tyrosine kinase inhibitor, in patients with advanced gastrointestinal stromal tumor (GIST).

Knowledge Generated

Ripretinib 150 mg daily (RP2D) was well tolerated in patients with advanced GIST; no maximum tolerated dose was reached. Preliminary efficacy in patients with advanced GIST was promising as second-, third-, and fourth-line or greater therapy.

Relevance

Our study results support the further development of ripretinib as an active and well-tolerated therapy in advanced GIST in the second-, third-, and fourth-line or greater, including the initiation of INVICTUS, a phase III study that showed significantly improved median progression-free survival with ripretinib compared with placebo as fourth-line or greater therapy in advanced GIST, and INTRIGUE, a phase III study currently evaluating ripretinib versus sunitinib as second-line therapy. In May 2020, ripretinib was approved by the US FDA for the treatment of adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib.

stabilize the kinase in the inactive state, preventing downstream signaling and cell proliferation.[19] This MoA provides broad inhibition of KIT/PDGFRA kinase activity, including *KIT/PDGFRA* wild type and multiple primary and secondary mutations. Ripretinib also inhibits other kinases in vitro, including PDGFRB, TIE2, VEGFR2, and BRAF.[19] A comparison of the MoA of ripretinib with that of other TKIs currently approved for the treatment of advanced GIST is provided in the Appendix (online only).

We report results from, to our knowledge, the first-in-human phase I study of ripretinib (ClinicalTrials.gov identifier: NCT02571036) in patients with advanced GIST and other malignancies with a focus on patients with GIST receiving 150 mg once daily.

PATIENTS AND METHODS

Patients

Patients were ≥ 18 years of age with a histologically confirmed diagnosis of GIST with a *KIT* or *PDGFRA* mutation and disease progression or intolerance to ≥ 1 line of systemic anticancer therapy or other malignancies with amplifications and/or mutations in *KIT* or *PDGFRA*, or other mutations that conferred sensitivity to ripretinib (eg, *PDGFRB*, *TIE2*, or *VEGFR2*). Initially, patients with *KIT/PDGFRA* wild-type mutational status were permitted; however, after protocol amendments, these patients were excluded. Other eligibility criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) of ≤ 2 and adequate organ function and bone marrow reserve. Complete inclusion and exclusion criteria are available in the Data Supplement.

Study Design

This was a multicenter phase I dose-escalation study of single-agent oral ripretinib with an expansion phase at the recommended phase II dose (RP2D). Primary objectives were to determine the safety and tolerability, maximum tolerated dose (MTD), and RP2D in the dose-escalation phase and to further evaluate safety and early efficacy in the dose-expansion phase. Secondary objectives included pharmacokinetic (PK) profile assessment. A pharmacologically guided 3 + 3 design was used to determine the MTD of ripretinib administered once or twice daily. Patients received ripretinib 20-200 mg twice a day or 100-250 mg once daily in repeated 28-day cycles until disease progression, unacceptable toxicity, or consent withdrawal. The MTD was defined as the highest dose level immediately below the dose level that resulted in dose-limiting toxicity (DLT) in ≥ 33% of patients during the first treatment cycle. If a dose level was declared safe (ie, zero DLTs in three patients or one DLT in six patients), the cohort may have been expanded to an additional six patients to further investigate PKs, pharmacodynamics, tolerability, or antitumor activity. Throughout the dose-escalation phase, data were routinely reviewed and monitored by a safety review team composed of principal investigators and key Deciphera personnel.

In the expansion phase, patients were enrolled into molecularly defined (*KIT* or *PDGFRA*) disease-specific cohorts, including GIST, and received the RP2D of ripretinib 150 mg once daily. Patients with GIST receiving ripretinib 150 mg once daily with disease progression were allowed to escalate to 150 mg twice a day after cycle 2; patient outcomes were collected according to the initial dose assigned. This article presents results focused on patients

with GIST in the expansion phase and those in the dose-escalation phase who received 150 mg once daily.

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 at each study site and by appropriate regulatory authorities before the start of the study.

Safety and Efficacy Assessments

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 at prespecified intervals (Data Supplement). Adverse events (AEs) were captured continuously from the signing of the informed consent until 30 days after the last administration of ripretinib 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 GIST receiving 150 mg once daily in the dose-escalation and expansion phases as a preplanned subanalysis. Tumor imaging was performed at screening, after cycles 2, 4, and 6, every three cycles thereafter, and at final study visit. Objective response in both phases was confirmed approximately

TABLE 1. Baseline Patient Characteristics for All Patients in the Dose-Escalation and Expansion Phases and Patients with GIST Receiving Ripretinib 150 mg Once Daily

		Ripretinib 150 mg Once Daily in Patients With GIST			
Characteristics	**All Patients[a] (N = 258)**	**Second Line (n = 31)**	**Third Line (n = 28)**	**Fourth Line or Greater (n = 83)**	**Total (n = 142)**
Age at study entry, years					
Mean (SD)	60.0 (12.7)	59.8 (11.9)	64.0 (8.3)	59.5 (11.9)	60.4 (11.4)
Median (range)	61.0 (19-92)	60.0 (32-80)	63.5 (48-82)	59.0 (27-87)	60.0 (27-87)
Age category, years					
≥ 18 to < 65	162 (62.8)	18 (58.1)	15 (53.6)	57 (68.7)	90 (63.4)
≥ 65	96 (37.2)	13 (41.9)	13 (46.4)	26 (31.3)	52 (36.6)
Sex					
Male	158 (61.2)	14 (45.2)	17 (60.7)	52 (62.7)	83 (58.5)
Female	100 (38.8)	17 (54.8)	11 (39.3)	31 (37.3)	59 (41.5)
Race/ethnicity					
American Indian or Alaskan native	3 (1.2)	0	0	3 (3.6)	3 (2.1)
Asian	15 (5.8)	2 (6.5)	1 (3.6)	6 (7.2)	9 (6.3)
Black or African American	20 (7.8)	4 (12.9)	2 (7.1)	7 (8.4)	13 (9.2)
White	206 (79.8)	25 (80.6)	25 (89.3)	63 (75.9)	113 (79.6)
Other	14 (5.4)	0	0	4 (4.8)	4 (2.8)
ECOG performance status					
0	93 (36.0)	16 (51.6)	13 (46.4)	38 (45.8)	67 (47.2)
1	152 (58.9)	15 (48.4)	15 (53.6)	42 (50.6)	72 (50.7)
2	13 (5.0)	0	0	3 (3.6)	3 (2.1)
Primary mutation[b] in patients with GIST receiving 150 mg once daily					
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)

NOTE. Data are presented as No. (%) unless otherwise noted.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha.

[a]All patients included patients with GIST, malignant glioma, systemic mastocytosis, melanoma, soft tissue sarcoma, other solid tumors, and renal impairment (GIST and other solid tumors).

[b]Determined by molecular pathology report.

28 days later and assessed by the investigator using RECIST version 1.1. An objective response rate (ORR) was defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR). Other efficacy end points included time to best response (defined as 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 PFS (time from cycle 1 day 1 to disease progression or death).

Pharmacokinetic Assessments

All PK samples were analyzed by a central laboratory. PK parameters included time to maximum observed concentration (T_{max}), maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), and half-life.

Statistical Analyses

Safety analyses were performed using the safety population (all patients who received a ripretinib dose). Clinical activity analyses, including efficacy, were performed using the intent-to-treat population (patients in the safety population, excluding two patients who only received one single ripretinib dose on day −7). PK analyses were performed on all patients in the safety population who had ≥ 1 PK concentration.

Baseline demographics, patient characteristics, plasma concentrations, and PK parameters were summarized using descriptive statistics. ORR was summarized using two-sided 95% exact binomial CIs. PFS and duration of response were summarized using the Kaplan-Meier method; time to response was summarized descriptively for confirmed responders.

RESULTS

From November 12, 2015 to August 31, 2019 (data cutoff), 258 patients (n = 184 GIST) were enrolled and received ≥ 1 dose of ripretinib during the dose-escalation (n = 68) and expansion (n = 190) phases (Appendix Fig A1, online only). At the time of data cutoff, 69 (26.7%) patients remained on study treatment (n = 12, dose-escalation phase; n = 57, expansion phase). Reasons for treatment discontinuation are listed in Appendix Table A1 (online only). The median (range) follow-up time was 6.2 (0.1-45.6) months. Overall baseline patient characteristics are listed in Table 1.

In the dose-escalation phase, the doses tested included 20 (n = 4), 30 (n = 4), 50 (n = 11), 100 (n = 12), 150 (n = 6), and 200 (n = 7) mg twice a day and 100 (n = 6), 150 (n = 12), and 250 (n = 6) mg once daily. Patients in the expansion phase received the RP2D of 150 mg once daily. A total of 142 patients with advanced GIST from both phases (n = 12, dose-escalation phase; n = 130, expansion phase) were initially assigned to receive ripretinib 150 mg once daily. Of those patients, 42 (29.6%) remained on treatment; 100 (70.4%) had discontinued treatment at data cutoff. Primary reasons for treatment discontinuation were similar to those in the overall group (Appendix Table A1). The median (range) follow-up time in patients with GIST receiving 150 mg once daily was 11.5 (0.1-33.0) months; baseline characteristics were similar to those of all patients (Table 1).

DLTs and MTD

Three DLTs were reported in the dose-escalation phase, with one each occurring in the 100 mg twice a day (n = 12), 200 mg twice a day (n = 7), and 150 mg once daily (n = 12) dose cohorts. At 100 mg twice a day, a DLT of asymptomatic grade 3 lipase elevation occurred. Ripretinib treatment was interrupted in this patient; the dose was reduced to 100 mg once daily and subsequently increased to 100 mg twice a day. At 200 mg twice a day, a DLT of asymptomatic grade 3 lipase elevation occurred, which normalized within 5 days, and the

TABLE 2. Summary of TEAEs by Line of Therapy in Patients With GIST Receiving Ripretinib 150 mg Once Daily

TEAE	Second Line (n = 31)	Third Line (n = 28)	Fourth Line or Greater (n = 83)	Total (N = 142)
Any TEAE	31 (100.0)	28 (100.0)	83 (100.0)	142 (100.0)
Any grade 3/4 TEAE	24 (77.4)	21 (75.0)	53 (63.9)	98 (69.0)
Any treatment-emergent SAE	16 (51.6)	14 (50.0)	49 (59.0)	79 (55.6)
Any drug-related TEAE	31 (100.0)	28 (100.0)	82 (98.8)	141 (99.3)
Any grade 3/4 drug-related TEAE	16 (51.6)	14 (50.0)	27 (32.5)	57 (40.1)
Any drug-related treatment-emergent SAE	6 (19.4)	2 (7.1)	10 (12.0)	18 (12.7)
Any TEAE leading to study treatment discontinuation	3 (9.7)	3 (10.7)	14 (16.9)	20 (14.1)
Any TEAE leading to study discontinuation	3 (9.7)	1 (3.6)	15 (18.1)	19 (13.4)
Any TEAE leading to death[a]	4 (12.9)	0	18 (21.7)	22 (15.5)

NOTE. Data are presented as No. (%).

Abbreviations: GIST, gastrointestinal stromal tumor; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a]TEAEs leading to death in second-line patients were primarily disease progression.

TABLE 3. Grades 1-4 TEAEs (regardless of drug relation) in > 15% of Patients With GIST Receiving Ripretinib 150 mg Once Daily in the Dose-Escalation and Expansion Phases

Preferred Term	Grade 1/2 (n = 142)	Grade 3/4 (n = 142)	Total Grades 1–4 (n = 142)
Any TEAE[a]	43 (30.3)	98 (69.0)	141 (99.3)
Alopecia[b]	88 (62.0)	—	88 (62.0)
Fatigue	74 (52.1)	4 (2.8)	78 (54.9)
Myalgia	69 (48.6)	0	69 (48.6)
Nausea	63 (44.4)	2 (1.4)	65 (45.8)
PPES	61 (43.0)	1 (0.7)[c]	62 (43.7)
Constipation	56 (39.4)	0	56 (39.4)
Decreased appetite	46 (32.4)	2 (1.4)	48 (33.8)
Diarrhea	44 (31.0)	3 (2.1)	47 (33.1)
Abdominal pain	29 (20.4)	13 (9.2)	42 (29.6)
Muscle spasms	42 (29.6)	0	42 (29.6)
Lipase increased	14 (9.9)	25 (17.6)	39 (27.5)
Weight decreased	39 (27.5)	0	39 (27.5)
Vomiting	37 (26.1)	1 (0.7)	38 (26.8)
Headache	36 (25.4)	1 (0.7)	37 (26.1)
Arthralgia	32 (22.5)	0	32 (22.5)
Dry skin	32 (22.5)	0	32 (22.5)
Hypertension	24 (16.9)	8 (5.6)	32 (22.5)
Anemia	19 (13.4)	10 (7.0)	29 (20.4)
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)
Hypophosphatemia	17 (12.0)	7 (4.9)	24 (16.9)
Rash	23 (16.2)	0	23 (16.2)
Seborrheic keratosis	23 (16.2)	0	23 (16.2)
Actinic keratosis	22 (15.5)	0	22 (15.5)

NOTE. Data are presented as No. (%).

Abbreviations: GIST, gastrointestinal stromal tumor; PPES, palmar-plantar erythrodysesthesia; TEAE, treatment-emergent adverse event.

[a]Patients may have experienced > 1 TEAE.

[b]Alopecia was reported in 88 patients, with a total of 108 alopecia events, including 72 mild and 36 moderate events. Per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, alopecia is only assessed as grade 1 or 2.

[c]PPES grade 3 was reported in 1 (0.7%) of 142 patients.

ripretinib dose was reduced to 150 mg twice a day. At 150 mg once daily, a DLT of asymptomatic grade 4 creatine phosphokinase increase occurred. Ripretinib treatment was held and then continued at a reduced dose of 100 mg once daily.

No MTD was reached, as < 33% of patients at each dose level experienced a DLT. The presumed threshold for efficacy for ripretinib is an $AUC_{0\text{-}24\ h}$ of 10,000 ng × h/mL (ripretinib and its active metabolite, DP-5439), which produced > 90% KIT inhibition in a preclinical murine cancer model and complete tumor growth inhibition at this target AUC. On the basis of in vivo and in vitro pharmacology studies predicting that 150 mg once daily was an efficacious dose, as well as interim PK analysis in this study, the ripretinib 150 mg once daily dose was predicted to maintain the PK exposure above this presumed threshold in > 90% of patients. In addition, exposure and safety data from the dose-escalation phase of this study supported the selection of the RP2D of 150 mg once daily in the expansion phase.

Safety and Efficacy of Ripretinib 150 mg Once Daily in Patients With GIST

Ripretinib was generally well tolerated in patients with advanced GIST receiving 150 mg once daily despite treatment-emergent adverse events (TEAEs) being

TABLE 4. Efficacy by Line of Therapy in Patients With GIST Receiving Ripretinib 150 mg Once Daily

Parameters	Second Line (n = 31)	Third Line (n = 28)	Fourth Line or Greater (n = 83)	Total (N = 142)
Best overall response, No. (%)[a]				
CR	0	0	0	0
PR, confirmed	6 (19.4)	4 (14.3)	6 (7.2)	16 (11.3)
Stable disease	21 (67.7)	18 (64.3)	48 (57.8)	87 (61.3)
Progressive disease	4 (12.9)	6 (21.4)	22 (26.5)	32 (22.5)
Not evaluable	0	0	1 (1.2)	1 (0.7)
No response assessment	0	0	6 (7.2)	6 (4.2)
ORR (95% CI), %	19.4 (7.5 to 37.5)	14.3 (4.0 to 32.7)	7.2 (2.7 to 15.1)	11.3 (6.6 to 17.7)
Duration of response, No.	6	4	6	16
No. of patients with event (disease progression)	3	1	3	7
Median (95% CI), months	18.4 (5.7 to 18.4)	NE (12.0 to NE)	17.5 (5.6 to NE)	18.4 (11.1 to NE)
Time to response				
Median (range), months	3.8 (1.7-8.2)	1.9 (1.8-5.7)	3.7 (1.8-13.6)	3.7 (1.7-13.6)
Duration of treatment[b]				
Median (range), months	14.8 (1.0-31.1)	11.7 (1.8-29.1)	6.8 (0.1-32.8)	10.6 (0.1-32.8)
PFS				
No. of censored patients	8	6	13	27
Median (95% CI), months	10.7 (5.5 to 13.8)	8.3 (5.5 to 11.1)	5.5 (3.6 to 6.2)	5.6 (5.5 to 8.2)

Abbreviations: CR, complete response; GIST, gastrointestinal stromal tumor; NE, not estimable; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

[a]Investigator response assessment.

[b]Sixty-four patients escalated to 150 mg twice a day among patients with GIST in the 150 mg once-daily dose group.

reported in 142 (100%) patients (Table 2). The most common overall TEAEs (> 15% of patients, regardless of drug relation) and corresponding grade 3/4 TEAEs are reported in Table 3. Treatment-emergent serious adverse events (regardless of drug relation) in > 3% of patients with GIST receiving 150 mg once daily included abdominal pain (n = 14 [9.9%]), death (n = 11 [7.7%]), cancer surgery (n = 7 [4.9%]), and sepsis (n = 6 [4.2%]). TEAEs leading to a dose reduction occurred in 26 (18.3%) patients, and TEAEs leading to treatment interruption occurred in 77 (54.2%) patients. Only eight (5.6%) patients with GIST receiving 150 mg once daily discontinued study treatment secondary to a drug-related TEAE. Safety data for all patients are included in the Appendix and in Appendix Table A2 (online only).

The mPFS was 10.7 months (95% CI, 5.5 to 13.8 months) for patients on second-line therapy, 8.3 months (95% CI, 5.5 to 11.1 months) for third-line, and 5.5 months (95% CI, 3.6 to 6.2 months) for fourth-line or greater therapy (Table 4; Fig 1). The probability of PFS at 12 months, by line of therapy, was 33.5% (95% CI, 17.6% to 50.1%), 29.2% (95% CI, 13.5% to 46.9%), and 21.2% (95% CI, 12.8% to 31.1%) for second-, third-, and fourth-line or greater therapy, respectively. ORRs for second-, third-, and fourth-line or greater therapies were 19.4% (n = 6/31), 14.3% (n = 4/28), and 7.2% (n = 6/83), respectively (Table 4). The best percentage change in target lesions in patients with GIST on second-, third-, or fourth-line or greater therapy is shown in Figure 2. The median time (range) to response among responders was 3.7 (1.7-13.6) months, and the median duration of response was 18.4 (95% CI, 11.1 to not estimable [NE]) months in the 16 responders receiving ripretinib 150 mg once daily, with nine patients continuing to respond as of the data cutoff. The median duration of response for patients on second-line therapy (n = 6) was 18.4 months and was NE for patients on third-line therapy (n = 4). In fourth-line or greater therapy, the median duration of response was 17.5 months in six responders, with three patients continuing to respond as of the data cutoff. As described in the methods, patients who experienced progression and continued to receive clinical benefit were allowed to stay on treatment with the option of dose escalation and therefore may have remained on treatment post progression. The median (range) duration of treatment of second-, third-, and fourth-line or greater therapy were 14.8 (1.0-31.1) months, 11.7 (1.8-29.1) months, and 6.8 (0.1-32.8) months, respectively.

Pharmacokinetics

Ripretinib was absorbed after single and multiple doses across the dose ranges studied (single doses from 20-250 mg; Appendix Table A3, online only) and multiple doses

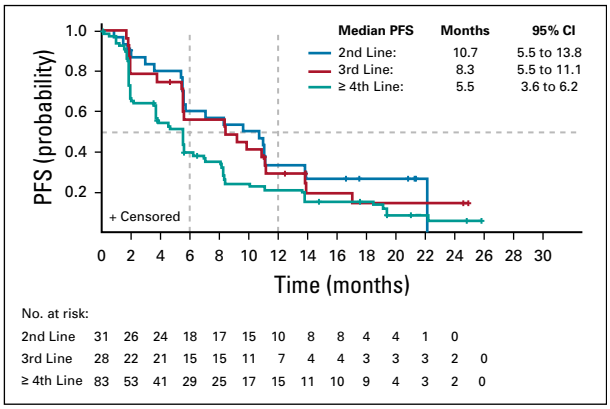

FIG 1. Kaplan-Meier plot of progression-free survival (PFS) by line of therapy in patients with gastrointestinal stromal tumors receiving an initially assigned dose of 150 mg once daily in dose-escalation and expansion phases.

from 20-200 mg twice a day; Tables A4 and A5, online only). The time to T_{max} ranged from 2-10 hours after single doses administered under fasting conditions on cycle 1 day 1. After a single dose of ripretinib 150 mg on cycle 1 day 1, mean C_{max} (coefficient of variation [CV%]), $AUC_{0\text{-}12h}$ (CV%), and $AUC_{0\text{-}24h}$ (CV%) were 502 ng/mL (56.8%), 3,773 ng × h/mL (58.3%), and 6634 ng × h/mL (59.8%), respectively. However, ripretinib PK parameters after single doses were highly variable between patients, with the CV% for C_{max} and $AUC_{0\text{-}24h}$ ranging from 35%-60% at ripretinib doses with PK data for at least 10 patients. In most patients, the terminal half-life on the basis of noncompartmental analysis could not be estimated with the PK sampling time points included in the protocol. At cycle 1 day 15, the mean C_{max} (CV%) and $AUC_{0\text{-}12h}$ (CV%) were 761 ng/mL (31.8%) and 5,678 ng × h/mL (32.1%), respectively, after administration of ripretinib 150 mg once daily. On the basis of $AUC_{0\text{-}12h}$, 66% accumulation was observed, whereas C_{max} was 61% higher compared with that at cycle 1 day 1 for ripretinib 150 mg once daily.

The exposure (ie, AUC) of DP-5439 (active metabolite of ripretinib) was approximately 49% of the parent ripretinib after single 150-mg doses and approximately 129% after 15 days of dosing at 150 mg once daily. After a single dose of ripretinib 150 mg on cycle 1 day 1, DP-5439 mean C_{max} (CV%), $AUC_{0\text{-}12h}$ (CV%), and $AUC_{0\text{-}24h}$ (CV%) were 231 ng/mL (63.4%), 1,710 ng × h/mL (63.6%), and 4,096 ng × h/mL (60.3%), respectively. At cycle 1 day 15, the DP-5439 mean C_{max} (CV%) and $AUC_{0\text{-}12h}$ (CV%) were 804 ng/mL (45.5%) and 7,138 ng × h/mL (44.4%), respectively, after administration of ripretinib 150 mg once daily; accumulation of DP-5439 was 4.6- to 5.3-fold.

DISCUSSION

Efficacy for second-line sunitinib and third-line regorafenib are limited, with an mPFS of approximately 5.6 months and ORR of 6.8% for sunitinib and an mPFS of 4.8 months and an ORR of 4.5% for regorafenib.[8,9] In addition, treatment with avapritinib is limited to GIST with *PDGFRA* exon 18 mutations.[17] Therefore, an unmet medical need remains for tolerable and effective targeted therapies in patients with imatinib-resistant advanced GIST. In this phase I study, ripretinib had a favorable safety profile and exhibited preliminary efficacy in advanced GIST.

In the dose-escalation phase of the study, the MTD was not reached. The assessment of the safety, PK, and preliminary pharmacodynamic data resulted in determination of an RP2D of ripretinib 150 mg once daily. This dose was further evaluated in the expansion phase. Safety and efficacy results for patients with GIST receiving ripretinib 150 mg once daily were combined from the dose-escalation and expansion phases. Ripretinib 150 mg once daily was generally well tolerated, with only eight of 142 (5.6%) patients discontinuing the study secondary to a drug-related TEAE. One of the most common TEAEs reported in patients with GIST receiving 150 mg once daily was alopecia, occurring in 88 (62.0%) patients, majority grade 1. The pathogenesis of ripretinib-associated alopecia is unclear but may be secondary to the inhibition of kinases associated with alopecia (eg, KIT, PDGRA, VEGFR2, BRAF).[19-21] Alopecia has been reported with other TKIs in patients with advanced GIST; however, the incidence in our study was higher.[9,17,22] Similarly, palmar-plantar erythrodysesthesia (PPES; reported with other TKIs as hand-foot skin reaction or hand-foot syndrome) was reported in 62 of 142 (43.7%) patients with GIST receiving ripretinib 150 mg once daily, with grade 3 in only one (0.7%) patient; no patients discontinued study treatment because of PPES. Syndromes such as PPES have been reported as grade 3 in 4% and 19.7% with sunitinib and regorafenib, respectively.[8,9]

Grade 3 or 4 lipase increase was reported in 25 (17.6%) patients with GIST receiving ripretinib 150 mg once daily and was typically asymptomatic and not clinically significant. The two patients with a DLT of lipase increased were asymptomatic, with no diagnosis of pancreatitis. In two separate patients receiving 150 mg once daily, pancreatitis was diagnosed based on abdominal pain and lipase elevation (mild pancreas inflammation on computed tomography scan in one patient). In both cases, symptoms and lipase elevation improved after a dosing interruption; ripretinib was restarted at a reduced dose in both cases without recurrence of pancreatitis. Although the mechanism of increased lipase levels in patients treated with TKIs is unclear, increases are also reported with other TKIs such as imatinib in patients with chronic myeloid leukemia and with regorafenib in patients with colorectal cancer.[14,22]

Preliminary efficacy results in patients with GIST receiving ripretinib 150 mg once daily showed promising activity across all lines of therapy included in this study. In patients receiving fourth-line or greater therapy, the ORR (all confirmed PR) was 7.2%; mPFS was 5.5 months. Early results of this study

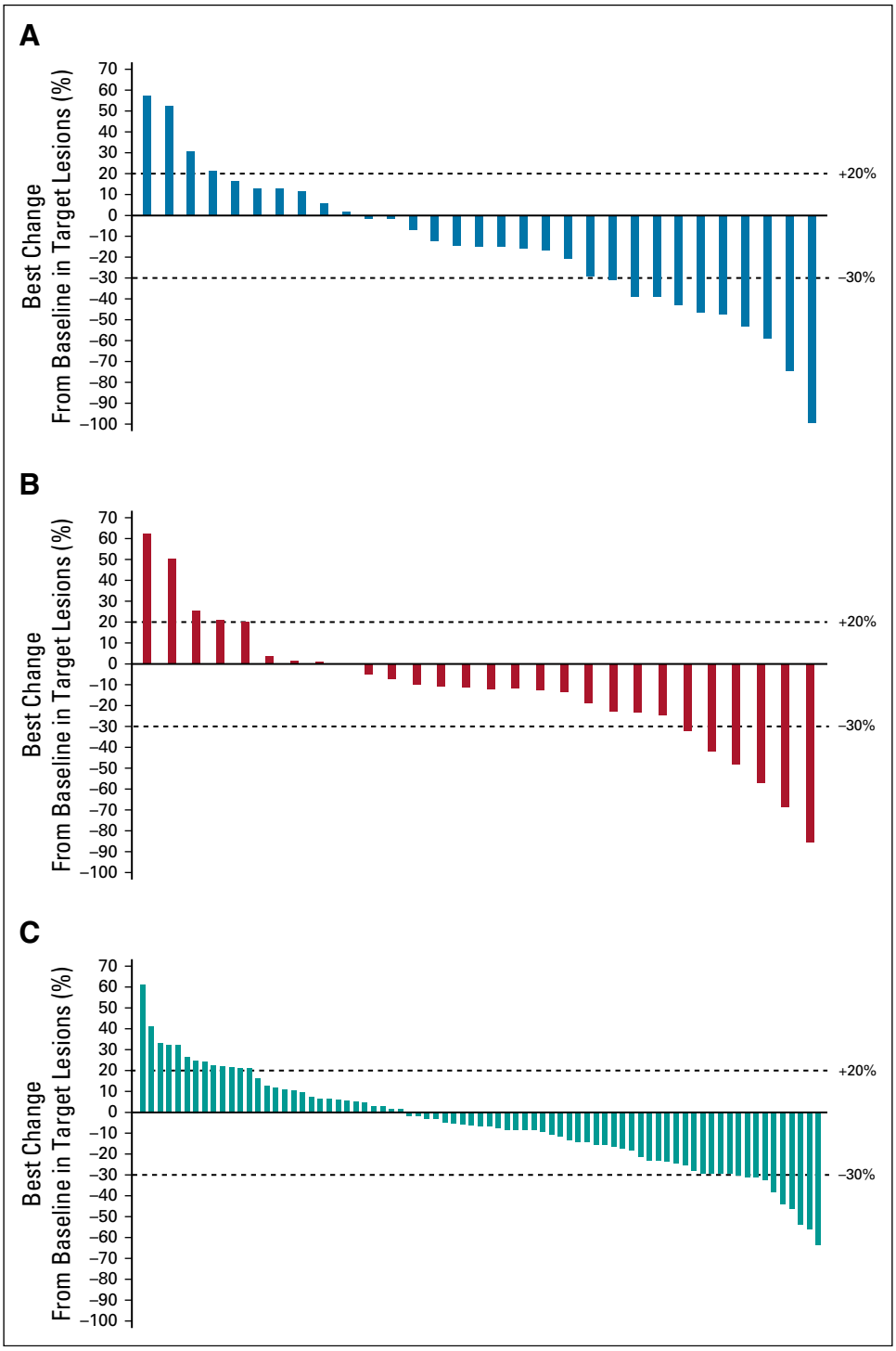

FIG 2. The best percentage change in target lesions in patients with gastrointestinal stromal tumors receiving ripretinib 150 mg once daily as (A) second-line therapy, (B) third-line therapy, or (C) fourth-line or greater therapy. The waterfall plot shows the best percentage change in target lesions regardless of confirmation of response.

supported the initiation of INVICTUS (ClinicalTrials.gov identifier: NCT0335373), a phase III study of ripretinib in patients with advanced GIST who experienced treatment failure with at least imatinib, sunitinib, and regorafenib.[23] INVICTUS demonstrated a significant improvement in mPFS compared with placebo (6.3 *v* 1 month, respectively; hazard ratio, 0.15; 95% CI, 0.09 to 0.25; $P < .0001$); the ORR was 9.4% versus 0.0% ($P = .0504$) for ripretinib and placebo, respectively. The ORR and mPFS reported in this phase I study for second-line (19.4% and 10.7 months) and third-line (14.3% and 8.3 months) therapies are encouraging. Although formal cross-trial comparisons are not possible, when taken in context of prior reports, ORR and PFS of ripretinib in this study exceed those historically reported in centrally read registrational trials for second-line sunitinib therapy (6.8% and approximately 5.6 months) and

third-line regorafenib therapy (4.5% and 4.8 months).[9,14,15] These results also support the ongoing phase III study (INTRIGUE; ClinicalTrials.gov identifier: NCT03673501) in which ripretinib is being evaluated as a second-line therapy compared with sunitinib in patients with advanced GIST.[24] In May 2020, the US FDA approved ripretinib for the treatment of adult patients with advanced GIST who have received previous treatment with three or more kinase inhibitors including imatinib.[25]

In summary, ripretinib has a favorable safety profile and demonstrated substantial promising efficacy in patients with advanced GIST previously treated with imatinib across all lines of therapy.

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CLINICAL TRIAL INFORMATION

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DATA AVAILABILITY STATEMENT

Deciphera will share the redacted Phase I study protocol in the Data Supplement. Qualified scientific and medical researchers may make requests for individual participant data that underlie the results (text, tables, figures, and appendices) reported in this article, after de-identification, at info@deciphera.com. Methodologically sound proposals for such data will be evaluated and approved by Deciphera in its sole discretion. All approved researchers must sign a data access agreement prior to accessing the data. Data will be available as soon as possible but no later than within 1 year of the acceptance of the article for publication, and for 3 years following article publication. Deciphera will not share identified participant data or a data dictionary.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Switch Control Inhibition of KIT and PDGFRA in Patients With Advanced Gastrointestinal Stromal Tumor: A Phase I Study of Ripretinib

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No other potential conflicts of interest were reported.

APPENDIX

Ripretinib Mechanism of Action

Similar to imatinib and regorafenib, ripretinib is a type II tyrosine kinase inhibitor (TKI) and binds to both the ATP hinge region and the adjacent allosteric pockets of the inactive kinase, stabilizing KIT and PDGFRA in inactive conformations. Ripretinib sterically blocks the activation loop from switching into an active conformation by binding to the switch pocket, as well as directly binding and stabilizing the activation loop in its inactive conformation. This dual binding mechanism allows for antagonism of activation loop mutations comparable with or exceeding that with type I inhibitors (bind in the ATP-binding pocket of the active kinase) like avapritinib. Sunitinib is a type II TKI in its binding to KIT but does not bind into the switch pocket, nor does it effectively antagonize activation loop mutations (Roskoski R Jr: Pharmacol Res 103:26-48, 2016).[8,19]

Overall Safety

Overall, ripretinib was well tolerated, despite 257 (99.6%) patients reporting a TEAE; 137 (53.1%) had a treatment-emergent serious adverse event (SAE), and 173 (67.1%) had a grade 3/4 TEAE. The most common TEAEs reported in > 15% of patients and corresponding grade 3/4 TEAEs are listed in Appendix Table A2. Treatment-emergent SAEs in > 3% of patients were abdominal pain (17 [6.6%]), death (16 [6.2%]), cancer surgery (10 [3.9%]), and dyspnea (8 [3.1%]). TEAEs leading to a dose reduction occurred in 38 (14.7%) patients, and TEAEs leading to treatment interruption occurred in 127 (49.2%) patients. Only 16 (6.2%) patients discontinued study treatment secondary to a drug-related TEAE.

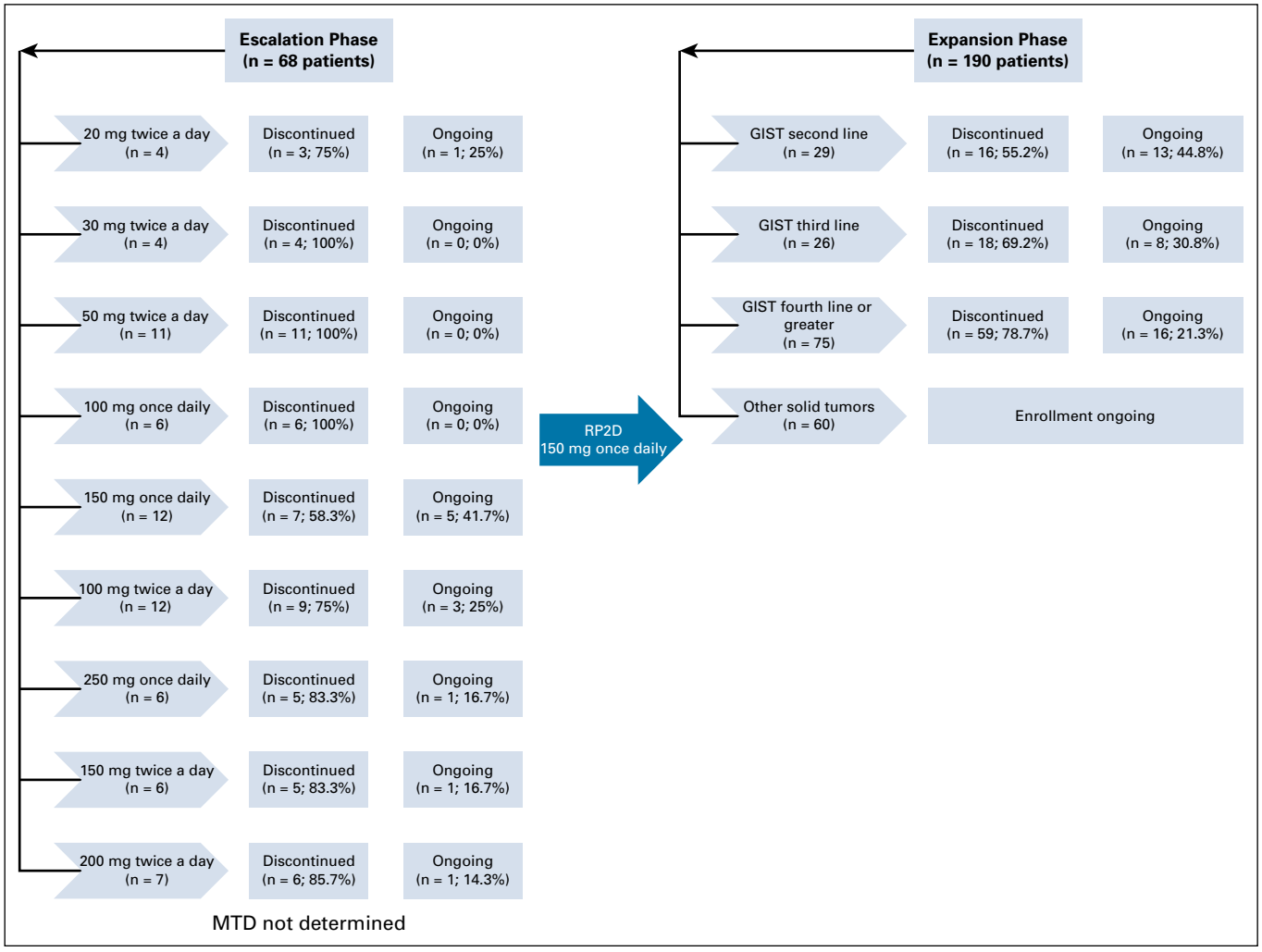

FIG A1. Study overview. GIST, gastrointestinal stromal tumor; MTD, maximum tolerated dose; RP2D, recommended phase II dose.

TABLE A1. Dispositions for All Patients and Patients With GIST Receiving Ripretinib 150 mg Once Daily

Disposition	All Patients (n = 258)	Ripretinib 150 mg Once Daily in Patients With GIST			
		Second Line (n = 31)	Third Line (n = 28)	Fourth Line or Greater (n = 83)	Total (N = 142)
Ongoing	69 (26.7)	14 (45.2)	9 (32.1)	19 (22.9)	42 (29.6)
Discontinued from treatment	189 (73.3)	17 (54.8)	19 (67.9)	64 (77.1)	100 (70.4)
Adverse event	25 (9.7)	1 (3.2)	2 (7.1)	9 (10.8)	12 (8.5)
Completed	0	0	0	0	0
Death	8 (3.1)	2 (6.5)	0	3 (3.6)	5 (3.5)
Lost to follow-up	1 (0.4)	0	0	0	0
Noncompliance with ripretinib	2 (0.8)	0	0	0	0
Physician decision	6 (2.3)	0	1 (3.6)	1 (1.2)	2 (1.4)
Progressive disease	103 (39.9)	12 (38.7)	14 (50.0)	30 (36.1)	56 (39.4)
Withdrawal by patient	18 (7.0)	0	1 (3.6)	8 (9.6)	9 (6.3)
Other	26 (10.1)	2 (6.5)	1 (3.6)	13 (15.7)	16 (11.3)

NOTE. Data are presented as No. (%).
Abbreviation: GIST, gastrointestinal stromal tumor.

TABLE A2. TEAEs in > 15% of All Patients and Corresponding Grade 3/4 TEAEs

		Twice-Daily Doses						Once-Daily Doses			
Preferred Term	**Grade**	**20 mg (n = 4)**	**30 mg (n = 4)**	**50 mg (n = 11)**	**100 mg (n = 12)**	**150 mg (n = 8)**	**200 mg (n = 7)**	**100 mg (n = 6)**	**150 mg (n = 200)**	**250 mg (n = 6)**	**All Patients (N = 258)**
Any TEAE	All	3 (75)	4 (100)	11 (100)	12 (100)	8 (100)	7 (100)	6 (100)	200 (100)	6 (100)	257 (99.6)
	3 and 4	2 (50.0)	2 (50.0)	8 (72.7)	9 (75.0)	4 (50.0)	3 (42.9)	4 (66.7)	136 (68.0)	5 (83.3)	173 (67.1)
Fatigue	All	2 (50)	4 (100)	7 (63.6)	7 (58.3)	5 (62.5)	4 (57.1)	3 (50.0)	96 (48.0)	4 (66.7)	132 (51.2)
	3 and 4	0	0	1 (9.1)	0	0	1 (14.3)	0	4 (2.0)	0	6 (2.3)
Alopecia	All	0	2 (50.0)	2 (18.2)	5 (41.7)	4 (50.0)	3 (42.9)	2 (33.3)	104 (52.0)	3 (50.0)	125 (48.4)
	3 and 4	—	—	—	—	—	—	—	—	—	—
Nausea	All	0	2 (50.0)	3 (27.3)	6 (50.0)	2 (25.0)	3 (42.9)	0	76 (38.0)	2 (33.3)	94 (36.4)
	3 and 4	0	0	0	0	0	0	0	2 (1.0)	0	2 (0.8)
Myalgia	All	0	1 (25.0)	2 (18.2)	4 (33.3)	4 (50.0)	0	1 (16.7)	76 (38.0)	3 (50.0)	91 (35.3)
	3 and 4	0	0	0	0	0	0	0	0	0	0
Constipation	All	0	2 (50.0)	3 (27.3)	4 (33.3)	2 (25.0)	1 (14.3)	1 (16.7)	69 (34.5)	2 (33.3)	84 (32.6)
	3 and 4	0	0	0	0	0	0	0	0	0	0
Decreased appetite	All	0	2 (50.0)	6 (54.5)	3 (25.0)	3 (37.5)	4 (57.1)	1 (16.7)	59 (29.5)	3 (50.0)	81 (31.4)
	3 and 4	0	0	0	0	0	0	1 (16.7)	2 (1.0)	0	3 (1.2)
PPES	All	0	0	0	3 (25.0)	4 (50.0)	3 (42.9)	0	67 (33.5)	3 (50.0)	80 (31.0)
	3 and 4	0	0	0	0	0	0	0	1 (0.5)	0	1 (0.4)
Diarrhea	All	1 (25.0)	2 (50.0)	4 (36.4)	2 (16.7)	3 (37.5)	3 (42.9)	0	58 (29.0)	1 (16.7)	74 (28.7)
	3 and 4	0	0	0	0	1 (12.5)	0	0	3 (1.5)	0	4 (1.6)
Lipase increased	All	2 (50.0)	1 (25.0)	3 (27.3)	6 (50.0)	1 (12.5)	1 (14.3)	1 (16.7)	53 (26.5)	3 (50.0)	71 (27.5)
	3 and 4	1 (25.0)	0	0	5 (41.7)	1 (12.5)	1 (14.3)	1 (16.7)	33 (16.5)	3 (50.0)	45 (17.4)
Weight decreased	All	0	1 (25.0)	3 (27.3)	1 (8.3)	4 (50.0)	5 (71.4)	1 (16.7)	48 (24.0)	2 (33.3)	65 (25.2)
	3 and 4	0	0	1 (9.1)	0	0	0	0	0	0	1 (0.4)
Vomiting	All	0	0	3 (27.3)	5 (41.7)	2 (25.0)	0	1 (16.7)	50 (25.0)	1 (16.7)	62 (24.0)
	3 and 4	0	0	0	0	1 (12.5)	0	0	1 (0.5)	0	2 (0.8)
Abdominal pain	All	1 (25.0)	2 (50.0)	2 (18.2)	2 (16.7)	2 (25.0)	2 (28.6)	1 (16.7)	47 (23.5)	2 (33.3)	61 (23.6)
	3 and 4	0	0	0	1 (8.3)	1 (12.5)	0	0	14 (7.0)	1 (16.7)	17 (6.6)
Muscle spasms	All	0	0	1 (9.1)	3 (25.0)	2 (25.0)	3 (42.9)	0	49 (24.5)	0	58 (22.5)
	3 and 4	0	0	0	0	0	0	0	0	0	0
Headache	All	0	1 (25.0)	1 (9.1)	1 (8.3)	3 (37.5)	0	1 (16.7)	47 (23.5)	0	54 (20.9)
	3 and 4	0	0	0	0	0	0	1 (16.7)	1 (0.5)	0	2 (0.8)
Anemia	All	0	3 (75.0)	3 (27.3)	4 (33.3)	3 (37.5)	0	1 (16.7)	38 (19.0)	1 (16.7)	53 (20.5)
	3 and 4	0	1 (25.0)	2 (18.2)	3 (25.0)	2 (25.0)	0	1 (16.7)	14 (7.0)	1 (16.7)	24 (9.3)
Dyspnea	All	0	4 (100)	4 (36.4)	4 (33.3)	1 (12.5)	2 (28.6)	1 (16.7)	35 (17.5)	1 (16.7)	52 (20.2)
	3 and 4	0	0	0	1 (8.3)	0	0	0	5 (2.5)	0	6 (2.3)
Hypertension	All	1 (25.0)	0	1 (9.1)	3 (25.0)	2 (25.0)	3 (42.9)	1 (16.7)	36 (18.0)	1 (16.7)	48 (18.6)
	3 and 4	1 (25.0)	0	1 (9.1)	2 (16.7)	1 (12.5)	1 (14.3)	1 (16.7)	10 (5.0)	1 (16.7)	18 (7.0)
Arthralgia	All	0	1 (25.0)	0	2 (16.7)	4 (50.0)	0	2 (33.3)	37 (18.5)	1 (16.7)	47 (18.2)
	3 and 4	0	0	0	0	0	0	0	0	0	0
Cough	All	0	0	2 (18.2)	4 (33.3)	2 (25.0)	3 (42.9)	0	29 (14.5)	2 (33.3)	42 (16.3)
	3 and 4	0	0	0	0	0	0	0	0	0	0

(continued on following page)

TABLE A2. TEAEs in > 15% of All Patients and Corresponding Grade 3/4 TEAEs (continued)

		Twice-Daily Doses						Once-Daily Doses			
Preferred Term	Grade	20 mg (n = 4)	30 mg (n = 4)	50 mg (n = 11)	100 mg (n = 12)	150 mg (n = 8)	200 mg (n = 7)	100 mg (n = 6)	150 mg (n = 200)	250 mg (n = 6)	All Patients (N = 258)
Dry skin	All	0	0	3 (27.3)	3 (25.0)	1 (12.5)	0	0	34 (17.0)	1 (16.7)	42 (16.3)
	3 and 4	0	0	0	0	0	0	0	0	0	0
Dizziness	All	0	3 (75.0)	2 (18.2)	2 (16.7)	0	1 (14.3)	0	29 (14.5)	2 (33.3)	39 (15.1)
	3 and 4	0	0	0	0	0	0	0	0	0	0

NOTE. Data are presented as No. (%).

Abbreviations: PPES, palmar-plantar erythrodysesthesia; TEAE; treatment-emergent adverse event.

TABLE A3. Geometric Mean (Geometric CV%) Plasma PK Parameter of Ripretinib After a Single Oral Dose in Patients With Advanced Malignancies in the Dose-Escalation Phase on Cycle 1 Day 1

	20 mg		30 mg		50 mg		100 mg		150 mg[a,b]		200 mg		250 mg	
Parameter	**Ripretinib (n = 3)**	**DP-5439 (n = 3)**	**Ripretinib (n = 4)**	**DP-5439 (n = 4)**	**Ripretinib (n = 10)**	**DP-5439 (n = 9)**	**Ripretinib (n = 18)**	**DP-5439 (n = 16)**	**Ripretinib (n = 24)**	**DP-5439 (n = 22)**	**Ripretinib (n = 6)**	**DP-5439 (n = 4)**	**Ripretinib (n = 6)**	**DP-5439 (n = 6)**
$AUC_{0\text{-}12h}$, ng × h/mL	835 (41.7%)	192 (22.7%)	917 (71.8%)	596 (106.6%)	2,415 (50.0%)	1,403 (64.7%)	3,493 (53.1%)	1,857 (80.3%)	3,773 (58.3%)	1,710 (63.6%)	3,625 (53.8%)	2,360 (35.6%)	9,113 (37.1%)	5,246 (43.0%)
$AUC_{0\text{-}24h}$, ng × h/mL	1,240 (37.1%)	268 (42.0%)	1,674 (89.5%	1,495 (134.5%)	3,826 (59.6%)	3,101 (83.0%)	7,275 (50.8%)	5,185 (84.9%)	6,634 (59.8%)	4,096 (60.3%)	5,617 (53.8%)	4,800 (39.4%)	14,842 (43.9%)	12,194 (71.4%)
$AUC_{0\text{-}t}$, ng × h/mL	1,240 (37.1%)	268 (42.0%)	1,674 (89.5%)	1,495 (134.5%)	3,826 (59.6%)	3,101 (83.0%)	7,275 (50.8%)	5,185 (84.9%)	6,634 (59.8%)	4,096 (60.3%)	5,617 (53.8%)	4,800 (39.4%)	14,842 (43.9%)	12,194 (71.4%)
C_{max}, ng/mL	109 (45.7%)	22.0 (32.1%)	133 (82.2%)	80.8 (173.7%)	339 (34.6%)	189 (97.1%)	500 (48.6%)	343 (88.6%)	502 (56.8%)	231 (63.4%)	525 (62.4%)	269 (44.0%)	1,070 (41.4%)	741 (49.9%)
T_{max}, hours, median (range)	4.00 (2.00-8.00)	6.00 (6.00-10.00)	2.04 (2.03-24.00)	24.12 (4.03-24.38	4.26 (2.00-6.17)	18.18 (4.03-25.62)	10.23 (2.00-24.68)	23.63 (3.83-24.68)	4 .02 (1.95-24.05)	15.6 (4.00-24.82)	2.08 (2.02-6.08)	6.22 (6.05-8.05)	6.03 (2.00-8.08)	9.04 (4.08-24.57)
M:P ratio $AUC_{0\text{-}t}$	0.2067 (12.3)		0.6225 (68.8)		0.5738 (55.1)		0.7048 (57.3)		0.4868 (58.7)		0.4582 (30.4)		0.7100 (38.9)	
M:P ratio C_{max}	0.2221 (75.1)		0.9184 (46.7)		0.8430 (35.2)		0.7298 (57.6)		0.6617 (53.1)		0.8975 (33.4)		0.8448 (48.1)	

Abbreviations: $AUC_{0\text{-}12h}$, area under the concentration-time curve from time 0-12 hours; $AUC_{0\text{-}24h}$, area under the concentration-time curve from time 0-24 hours; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last quantifiable concentration; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; M:P, metabolite to parent ratio; PK, pharmacokinetic; $T_{max.}$ time to maximum plasma concentration.

[a]Patients from once daily cohort and patients from twice a day cohort received only a single dose at Cycle 1 Day 1.

[b]Dose escalation and expansion combined.

TABLE A4. Geometric Mean (Geometric CV%) Plasma PK Parameters of Ripretinib After Multiple Once-Daily Doses in Patients With Advanced Malignancies in the Dose-Escalation Phase on Cycle 1 Day 15

	100 mg Once Daily		150 mg Once Daily[a]		250 mg Once Daily	
Parameter	**Ripretinib (n = 5)**	**DP-5439 (n = 5)**	**Ripretinib (n = 11)**	**DP-5439 (n = 12)**	**Ripretinib (n = 5)**	**DP-5439 (n = 5)**
$AUC_{0\text{-}12h}$, ng × h/mL	3,077 (95.7%) (n = 4)	3,346 (251.6%) (n = 4)	5,678 (32.1%) (n = 11)	7,138 (44.4%) (n = 11)	6,488 (22.8%) (n = 5)	6,439 (163.6%) (n = 5)
$AUC_{0\text{-}t}$, ng × h/mL	3,212 (80.2%) (n = 5)	3,545 (187.9%) (n = 5)	5,678 (32.1) (n = 11)	7,138 (44.4%) (n = 11)	6,488 (22.8%) (n = 5)	6,439 (163.6%) (n = 5)
C_{max}, ng/mL	505 (71.8%) (n = 5)	471 (218.9%) (n = 5)	761 (31.8%) (n = 11)	804 (45.5%) (n = 11)	888 (18.1%) (n = 5)	813 (120.5%) (n = 5)
T_{max}, hours, median (range)	2.00 (0.90-2.00) (n = 5)	4.00 (0.90-5.83) (n = 5)	2.08 (1.02-8.13) (n = 11)	6.00 (1.02-8.13) (n = 11)	4.05 (2.03-6.13) (n = 5)	6.18 (4.05-8.05) (n = 5)
C_{trough}, ng/mL	173 (184.7%) (n = 5)	291 (358.4%) (n = 5)	284 (62.5%) (n = 12)	546 (78.2%) (n = 12)	178 (107.2%) (n = 5)	287 (546.6%) (n = 5)
C_{avg}, ng/mL	256 (95.7%) (n = 4)	279 (251.6%) (n = 4)	473 (32.1%) (n = 11)	595 (44.4%) (n = 11)	541 (22.8%) (n = 5)	537 (163.6%) (n = 5)
RA $AUC_{0\text{-}12}$	0.997 (48.4%) (n = 4)	1.60 (152.9%) (n = 3)	1.66 (55.3%) (n = 11)	5.29 (48.7%) (n = 9)	0.634 (35.9%) (n = 5)	1.13 (101.1%) (n = 5)
RA C_{max}	1.12 (38.5%) (n = 5)	1.84 (116.3%) (n = 4)	1.61 (52.6%) (n = 11)	4.57 (34.5%) (n = 9)	0.725 (34.6%) (n = 5)	0.968 (74.9%) (n = 5)
M:P ratio $AUC_{0\text{-}t}$	1.14 (80.6) (n = 5)		1.29 (47.9) (n = 11)		1.02 (122.1) (n = 5)	
M:P ratio C_{max}	0.960 (90.4) (n = 5)		1.09 (48.0) (n = 11)		0.941 (103.2) (n = 5)	

Abbreviations: $AUC_{0\text{-}12h}$, area under the concentration-time curve from time 0-12 hours; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last measurable concentration; C_{avg}, average concentration; C_{max}, maximum observed plasma concentration; C_{trough}, observed concentration at the end of a dosing interval; CV, coefficient of variation; M:P, metabolite to parent ratio; PK, pharmacokinetic; RA, accumulation ratio; T_{max}, time to maximum plasma concentration.

[a]Dose escalation and expansion combined.

TABLE A5. Geometric Mean (Geometric CV%) Plasma PK Parameters of Ripretinib After Multiple Twice-a-Day Doses in Patients With Advanced Malignancies in the Dose-Escalation Phase on Cycle 1 Day 15

	20 mg Twice a Day		30 mg Twice a Day		50 mg Twice a Day		100 mg Twice a Day		150 mg Twice a Day		200 mg Twice a Day	
Parameter	**Ripretinib (n = 3)**	**DP-5439 (n = 3)**	**Ripretinib (n = 4)**	**DP-5439 (n = 4)**	**Ripretinib (n = 8)**	**DP-5439 (n = 8)**	**Ripretinib (n = 10)**	**DP-5439 (n = 10)**	**Ripretinib (n = 6)**	**DP-5439 (n = 6)**	**Ripretinib (n = 4)**	**DP-5439 (n = 4)**
$AUC_{0\text{-}12}$, ng × h/mL	1,514 (4.4%) (n = 2)	652 (7.8%) (n = 2)	1,891 (87.4%) (n = 3)	3,110 (249%) (n = 3)	4,073 (60.1%) (n = 5)	8,801 (76%) (n = 5)	6,777 (57.0%) (n = 10)	11,858 (85.5%) (n = 10)	7,929 (97.7%) (n = 5)	15,646 (110.3%) (n = 5)	5,841 (60.3%) (n = 4)	10,447 (78.9%) (n = 4)
$AUC_{0\text{-}t}$, ng × h/mL	1,408 (13.0%) (n = 3)	474 (60.2%) (n = 3)	2,325 (85.5%) (n = 4)	4,041 (197.7%) (n = 4)	4,645 (52.1%) (n = 8)	9,780 (63.9%) (n = 8)	6,777 (57.0%) (n = 10)	11,858 (85.5%) (n = 10)	8,614 (88.4%) (n = 6)	15,221 (94.8%) (n = 6)	5,841 (60.3%) (n = 4)	10,447 (78.9%) (n = 4)
C_{max}, ng/mL	207 (6.0%) (n = 3)	61.1 (49.3%) (n = 3)	355 (72.4%) (n = 4)	479 (182.5%) (n = 4)	675 (53.6%) (n = 8)	1,090 (63.4%) (n = 8)	913 (55.4%) (n = 10)	1,340 (81%) (n = 10)	1,290 (79.1%) (n = 6)	1,800 (85.9%) (n = 6)	805 (67.7%) (n = 4)	1,120 (69.4%) (n = 4)
T_{max}, hours, median (range)	2.00 (2.00-4.00) (n = 3)	2.00 (2.00-4.00) (n = 3)	1.97 (1.03-3.98) (n = 4)	3.01 (1.93-4.08) (n = 4)	2.02 (0.55-4.12) (n = 8)	2.03 (0.50-4.08) (n = 8)	3.09 (2.00-9.97) (n = 10)	4.27 (2.03-9.97) (n = 10)	2.01 (0.55-6.00) (n = 6)	4.01 (2.03-8.17) (n = 6)	1.04 (0.60-1.13) (n = 4)	6.06 (2.10-8.03) (n = 4)
C_{trough}, ng/mL	120 (41.0%) (n = 2)	38.0 (70.3%) (n = 2)	200 (105.8%) (n = 4)	395 (182.4%) (n = 4)	485 (48.2%) (n = 8)	1,035 (62.5%) (n = 8)	558 (72.2%) (n = 10)	1,097 (94.6%) (n = 10)	968 (113.8%) (n = 6)	1,590 (93.8%) (n = 6)	648 (69.5%) (n = 4)	1,008 (71.9%) (n = 4)
C_{avg}, ng/mL	126 (4.4%) (n = 2)	54.3 (7.8%) (n = 2)	158 (87.4%) (n = 3)	259 (249%) (n = 3)	339 (60.1%) (n = 5)	733 (76%) (n = 5)	565 (57.0%) (n = 10)	988 (85.5%) (n = 10)	661 (97.7%) (n = 5)	1,300 (110.3%) (n = 5)	487 (60.3%) (n = 4)	871 (78.9%) (n = 4)
RA ($AUC_{0\text{-}12}$)	2.20 (36.0%) (n = 2)	3.85 (9.3%) (n = 2)	2.66 (27.1%) (n = 3)	6.54 (54.8%) (n = 3)	2.04 (40.4%) (n = 5)	7.21 (50.3%) (n = 4)	2.08 (97.7%) (n = 10)	5.28 (87.9%) (n = 9)	2.41 (24.7%) (n = 5)	7.18 (40.5%) (n = 5)	2.11 (55.7%) (n = 4)	4.12 (95.8%) (n = 3)
RA (C_{max})	1.89 (44.4%) (n = 3)	2.78 (91.1%) (n = 3)	2.66 (16.9%) (n = 4)	5.93 (19.4%) (n = 4)	1.95 (36.5%) (n = 8)	5.28 (64.4%) (n = 7)	1.82 (108.7%) (n = 10)	2.89 (68.2%) (n = 9)	2.84 (17.9%) (n = 6)	7.36 (44.6%) (n = 6)	2.00 (87.6%) (n = 4)	4.17 (101.3%) (n = 3)
M:P ratio $AUC_{0\text{-}t}$	0.3458 (44.8) (n = 2)		1.787 (70.6) (n = 3)		2.165 (30.0) (n = 5)		1.799 (90.3) (n = 10)		1.817 (106.3) (n = 6)		1.839 (18.8) (n = 4)	
M:P ratio C_{max}	0.3031 (50.5) (n = 2)		1.386 (63.4) (n = 3)		1.667 (29.4) (n = 5)		1.507 (86.9) (n = 10)		1.442 (105.6) (n = 6)		1.428 (7.1) (n = 4)	

Abbreviations: $AUC_{0\text{-}12h}$, area under the concentration-time curve from time 0-12 hours; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last measurable concentration; C_{avg}, average concentration; C_{max}, maximum observed plasma concentration; C_{trough}, observed concentration at the end of a dosing interval; CV, coefficient of variation; M:P, metabolite to parent ratio; PK, pharmacokinetic; RA, accumulation ratio; T_{max}, time to maximum plasma concentration.