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George, S.; Chi, P.; Heinrich, M.C.; Mehren, M. von; Jones, R.L.; Ganjoo, K.; ... ; Janku, F.

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Original Research

Ripretinib inpatient dose escalation after disease progression provides clinically meaningful outcomes in advanced gastrointestinal stromal tumour



Suzanne George^a, Ping Chi^b, Michael C. Heinrich^c, Margaret von Mehren^d, Robin L. Jones^e, Kristen Ganjoo^f, Jonathan Trent^g, Hans Gelderblom^h, Albiruni A. Razakⁱ, Michael S. Gordon^j, Neeta Somaiah^k, Julia Jennings^l, Julie Meade^l, Kelvin Shi^l, Ying Su^l, Rodrigo Ruiz-Soto^l, Filip Janku^{m,*}

^a Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, United States

^b Human Oncology and Pathogenesis Program and Department of Medicine, Memorial Sloan Kettering Cancer Center, and Department of Medicine, Weill Cornell Medical College, New York, NY, United States

^c Hematology/Medical Oncology, VA Health Care System and OHSU Knight Cancer Institute, Portland, OR, United States

^d Hematology Oncology, Fox Chase Cancer Center, Philadelphia, PA, United States

^e Royal Marsden and Institute of Cancer Research, London, United Kingdom

^f Medical Oncology, Stanford University, Stanford, CA, United States

^g Medical Oncology, Sylvester Comprehensive Cancer Center/University of Miami, Miami, FL, United States

^h Medical Oncology, Leiden University Medical Center, Leiden, Netherlands

ⁱ Toronto Sarcoma Program, Princess Margaret Cancer Centre, Toronto, ON, Canada

^j HonorHealth Research Institute, Scottsdale, AZ, United States

^k Sarcoma Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

^l Deciphera Pharmaceuticals, LLC, Waltham, MA, United States

^m Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

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Gastrointestinal stromal tumours;

Abstract Purpose: Ripretinib is a switch-control tyrosine kinase inhibitor that broadly inhibits KIT and platelet-derived growth factor receptor α kinase signalling. Ripretinib showed preliminary efficacy in patients with advanced gastrointestinal stromal tumour (GIST) in a

* Corresponding author: 1515 Holcombe Blvd. Unit 455, Houston, TX, 77030, United States.

E-mail address: Suzanne_George@dfci.harvard.edu (S. George), chip@mskcc.org (P. Chi), heinrich@ohsu.edu (M.C. Heinrich), Margaret.vonMehren@fcc.edu (M. von Mehren), Robin.Jones@rmh.nhs.uk (R.L. Jones), kganjoo@stanford.edu (K. Ganjoo), JTrent@med.miami.edu (J. Trent), A.J.Gelderblom@lumc.nl (H. Gelderblom), Albiruni.Razak@uhn.ca (A.A. Razak), mgordon@honorhealth.com (M.S. Gordon), Nsomaiah@mdanderson.org (N. Somaiah), JJennings@Deciphera.com (J. Jennings), jmeade@deciphera.com (J. Meade), kshi@deciphera.com (K. Shi), Ysu@Deciphera.com (Y. Su), rruizsoto@deciphera.com (R. Ruiz-Soto), fjanku@me.com (F. Janku).

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Ripretinib;
Pharmacology;
Disease progression;
Progression-free
survival

phase I study across a range of doses. Results were confirmed in the phase III INVICTUS study, and ripretinib 150 mg once daily (QD) was subsequently approved as a \geq fourth-line therapy. Here, we report the phase I study results of inpatient dose escalation (IPDE) in patients with GIST treated across second, third and later lines of therapy.

Methods: Patients with advanced GIST who experienced disease progression (PD) at ripretinib 150 mg QD could dose escalate to 150 mg twice daily (BID). Progression-free survival (PFS) 1 was calculated from the date of the first dose of ripretinib 150 mg QD to PD (as per Response Evaluation Criteria in Solid Tumours 1.1); PFS2 was from the date of IPDE (150 mg BID) to PD or death. Treatment-emergent adverse events (TEAEs) were summarised by dosing periods and compared descriptively.

Results: Of 142 patients with GIST receiving ripretinib 150 mg QD, 67 underwent IPDE. IPDE provided benefit across all lines of therapy; the median PFS2 was 5.6, 3.3 and 4.6 months for patients on second-, third- and \geq fourth-line therapy, respectively. A partial metabolic response after IPDE was demonstrated in 13 of 37 patients with available positron emission tomography scans. TEAEs reported at both doses were similar.

Conclusion: Ripretinib IPDE after PD provided continued clinical benefit in advanced GIST across second, third and later lines of therapy with a similar safety profile to that observed with the QD regimen.

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1. Introduction

Most gastrointestinal stromal tumours (GISTs) harbour an activating mutation in either KIT or platelet-derived growth factor receptor α (PDGFRA) tyrosine kinases [1–3]. Treatment of advanced GIST improved greatly with approval of oral tyrosine kinase inhibitors (TKIs). Five TKIs are approved for GIST in the United States—imatinib (adjuvant and first-line therapy), sunitinib (second-line therapy), regorafenib (third-line therapy), ripretinib (fourth-line therapy) and avapritinib (PDGFRA exon 18 mutant GIST) [4–7]. Although these TKIs improved the outcomes of patients with GIST, disease progression still occurs, with progression-free survival (PFS) being typically shorter after first-line treatment. Disease progression is largely due to the development of secondary mutations in *KIT* or *PDGFRA*, [8] which can result in complex intratumour and intertumour heterogeneity [8,9]. Thus, there is a need for therapeutic options in advanced GIST that are effective against a broad spectrum of *KIT* and *PDGFRA* mutations and provide clinical benefit beyond disease progression.

Ripretinib, approved for use based on the results of the phase III INVICTUS trial [10], is indicated in the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib [5,11,12]. Ripretinib, an oral switch-control TKI, has a unique dual mechanism of action that regulates the kinase switch pocket and activation loop [13]. This novel mechanism of action provides broad inhibition of KIT or PDGFRA kinase activity, including wild-type KIT or PDGFRA and multiple KIT and PDGFRA mutations [13]. In the

primary report of the phase I trial, ripretinib demonstrated promising efficacy and had a favourable safety profile in patients with advanced GIST treated across multiple lines of therapy [14]. Although no maximum tolerated dose (MTD) was reached, the recommended dose of ripretinib was established as 150 mg once daily (QD) based on safety, pharmacokinetic findings and pharmacodynamic findings [14].

Inpatient dose escalation (IPDE), as an alternative therapeutic option after disease progression while on an approved TKI, was previously demonstrated in patients receiving imatinib who, after progression, were allowed to cross over to a higher dose with benefit to a subset of patients [15]. A similar approach was explored in the ripretinib phase I study; on disease progression with ripretinib 150 mg QD, patients could dose escalate to ripretinib 150 mg twice daily (BID). Here, we report the efficacy, pharmacokinetics (PK) and safety results of IPDE in patients with advanced GIST treated across multiple lines of therapy from the phase I study.

2. Materials and methods

2.1. Study design and treatment

Detailed methods of the phase I study (NCT02571036) that included dose escalation and expansion phase have been previously described [14]. The escalation phase evaluated increasing doses of ripretinib administered in 28-day cycles in patients with advanced malignancies [14]. This escalation phase resulted in the recommended dose of 150 mg QD [14]. In the expansion phase, patients were enrolled into disease-specific cohorts,

including the KIT/PDGFR α mutant GIST cohort, and started on the recommended 150 mg QD dose of ripretinib [14]. The GIST cohort consisted of patients treated with 1 (second-line therapy), 2 (third-line therapy) or ≥ 3 (fourth-line or greater therapy) prior anti-cancer therapies [14]. Patients who progressed on ripretinib 150 mg QD, as determined by Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 and based on local radiology review, were given the option to escalate to 150 mg BID.

This study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent to participate in the study. Before the start of and throughout the study, the protocol, protocol amendments and informed consent documents were approved by each site's institutional review board and the appropriate regulatory authorities.

2.2. Patient population

Eligible patients included those ≥ 18 years of age with histologically confirmed advanced GIST [14]. Patients must have had ≥ 1 measurable lesion, as per RECIST version 1.1. For inclusion in the trial, patients with GIST were required to have a KIT or PDGFR α mutation and must have progressed on, or had intolerance to, at least 1 line of systemic TKIs. Baseline characteristics, including age, sex, Eastern Cooperative Oncology Group status and mutation status, were recorded. Full eligibility criteria are listed in [Supplementary Data](#).

2.3. Efficacy assessments

The primary efficacy outcome was PFS as per RECIST v1.1 based on local radiology review. PFS1 was calculated from the date of the first dose of ripretinib 150 mg QD to disease progression. PFS2 was defined as PFS on ripretinib 150 mg BID from the date of escalation to progression or death. An exploratory assessment of metabolic tumour response by ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET), as per European Organisation for Research and Treatment of Cancer (EORTC) criteria, was also conducted during the PFS2 period after the patient's initial progression. PFS2 baseline PET scans were taken within 10 days before IPDE; a follow-up scan was taken 17–31 days after IPDE. PET scans were assessed by a central reviewer.

2.4. Pharmacokinetic assessments

The PK of ripretinib and its active metabolite DP-5439 was assessed. PK sampling was conducted predose on day 15 during cycle 1, the first day of each subsequent cycle and at the final study visit. PK analyses are presented as the geometric mean predose steady state

trough plasma concentration of ripretinib and active metabolite DP-5439 at the 150 mg QD and 150 mg BID dose. The steady state was defined as when the regimen was administered $>50\%$ of the time for the specified interval (i.e. the 150 mg BID dose was administered most of the time during the IPDE period) and regimens for which the average number of days administered was ≥ 5 days (i.e. the patient is conceivably dosed to a steady state for each observed trough concentration). Plasma samples were analysed for ripretinib and DP-5439 concentrations by a validated high-performance liquid chromatography tandem mass spectrometric method.

2.5. Safety outcomes

Treatment-emergent adverse events (TEAEs) were defined as any AE that occurred after administration of the first dose of the study drug and through 30 days after the last dose of the study drug, any event that was considered drug-related, regardless of the start date of the event, any event that was present at baseline but worsened in severity or any event that was subsequently considered drug-related by the investigator. AEs were coded with MedDRA dictionary v21.1. AEs are presented for patients with GIST who received ripretinib 150 mg QD and dose escalated to 150 mg BID.

2.6. Statistical analyses

Analyses were conducted by the line of therapy (second, third and fourth or greater). Descriptive statistics were used to summarise continuous variables, and discrete variables were summarised using frequencies and percentages. For PFS, the Kaplan-Meier method was used to obtain non-parametric estimates, the associated 2-sided 95% confidence intervals (CIs) for the median survival time, the 25th and 75th percentiles and survival probability functions.

3. Results

3.1. Patients

As of 8th May 2020 (data cutoff), of 142 enrolled patients with advanced GIST receiving ripretinib 150 mg QD, 67 patients dose escalated to ripretinib 150 mg BID after disease progression ([Supplemental Fig. 1](#)). The IPDE population ($n = 67$) included 10 patients on second-line therapy, 17 patients on third-line therapy and 40 patients on fourth-line or greater therapy. Overall baseline patient characteristics are listed in [Table 1](#).

3.2. Efficacy

In the IPDE population, the median PFS1 (mPFS1; 150 mg QD) was 11.0 months (95% CI, 3.5, 22.1

Table 1
Baseline characteristics of the IPDE population.

Characteristics	Second line (n = 10)	Third line (n = 17)	≥Fourth line (n = 40)	Total (N = 67)
Age at informed consent (years)				
Mean (SD)	59.6 (13.57)	64.6 (8.66)	59.9 (10.03)	61.1 (10.35)
Median	60.0	64.0	59.0	60.0
Range	32, 80	51, 82	39, 87	32, 87
Age category (years)				
≥18–≤64	6 (60)	9 (53)	30 (75)	45 (67)
≥65	4 (40)	8 (47)	10 (25)	22 (33)
Sex				
Male	3 (30)	10 (59)	30 (75)	43 (64)
Female	7 (70)	7 (41)	10 (25)	24 (36)
ECOG status				
0	8 (80)	9 (53)	19 (48)	36 (54)
1	2 (20)	8 (47)	20 (50)	30 (45)
2	0	0	1 (3)	1 (2)
Primary mutations				
KIT exon 11	8 (80)	12 (71)	28 (70)	48 (72)
KIT exon 9	1 (10)	5 (29)	8 (20)	14 (21)
KIT other exons	0	0	2 (5)	2 (3)
PDGFRA (exon 18, non-D842V)	1 (10)	0	2 (5)	3 (5)

Data presented as n (%) unless otherwise indicated. Percentages were rounded to the nearest whole number.

ECOG, Eastern Cooperative Oncology Group; IPDE, inpatient dose escalation; PDGFRA, platelet-derived growth factor receptor alpha; SD, standard deviation.

months) for patients on second-line therapy, 8.3 months (95% CI, 1.8, 11.1 months) for third-line therapy and 5.5 months (95% CI, 2.1, 8.1 months) for fourth-line or greater therapy (Fig. 1A). After IPDE, the median PFS2 (mPFS2) was 5.6 months (95% CI, 1.4, not estimable) for patients on second-line therapy, 3.3 months (95% CI, 2.3, 7.4 months) for third-line therapy and 4.6 months (95% CI, 2.8, 5.6 months) for fourth-line or greater therapy (Fig. 1B). The ratio of mPFS2/mPFS1 in patients with GIST was 51%, 40% and 84% for second-line, third-line and fourth-line or greater therapy, respectively. Treatment duration for both dosing periods is shown in Fig. 2. Within the IPDE population, across all lines of therapy, 14 patients with advanced GIST were on treatment for 2 years or longer. At the time of data cutoff, 10 patients were continuing treatment, including 4 who showed disease progression at a higher dose of ripretinib but continued treatment for clinical benefit.

A total of 37 patients underwent pre-/post-escalation PET scans within the window. Assessment of tumour metabolic response as per EORTC criteria in patients with GIST who underwent IPDE (n = 37) was performed. A total of 13 (35.1%) patients, across all lines of therapy, demonstrated partial metabolic response, and 19 (51.4%) showed metabolic stable disease after dose escalation to ripretinib 150 mg BID compared with the baseline. A summary of the best overall response by the

line of therapy is shown in Supplemental Table 2. Radiological images of a partial metabolic response (−33.7% change in standardised uptake values) before and after dose escalation from a patient in this study are shown in Fig. 3.

3.3. Pharmacokinetics

PK analysis (n = 60) revealed that subsequent dose escalation from 150 mg QD to BID resulted in an approximately 2-fold increase in the steady state trough concentration of ripretinib and its active metabolite DP-5439. Patients who were missing or had an invalid steady state trough samples at either regimen (QD or IPDE) were excluded from the PK analysis. Geometric mean trough concentrations for ripretinib increased from 323 ng/mL at 150 mg QD to 676 ng/mL at 150 mg BID, whereas DP-5439 increased from 721 ng/mL to 1270 ng/mL after dose escalation.

3.4. Safety

The AE profile was similar during both dosing periods in patients with advanced GIST. TEAEs that occurred in >10% of the IPDE population during the IPDE period are listed in Table 2, with the corresponding TEAE frequencies during the QD dosing period provided for reference. Of note, only TEAEs that were new or worsened during the IPDE period are listed for that time period. Two TEAEs were notably higher in the IPDE period than those in the QD period, anaemia (22.4% vs. 4.5%) and dyspnoea (13.4% vs. 7.5%). No new TEAEs (>10%) were observed in the IPDE period, although two grade 3/4 AEs (>5% of patients)—abdominal pain (10.4%) and anaemia (6%)—were observed in the IPDE period only. Of 67 IPDE patients, 32 (47.8%) developed a grade 3/4 TEAE during the QD dosing period and 42 (62.7%) developed a grade 3/4 TEAE during the IPDE period. Twelve (17.9%) patients experienced a TEAE that led to death, none of which were considered related to the study drug.

Similar numbers of patients underwent dose reduction/interruptions because of TEAEs in both dosing periods. A summary of dose modifications that occurred during both dosing periods is presented in Table 3. After dose escalation to ripretinib 150 mg BID, 10 (15%) patients experienced TEAEs that led to treatment discontinuation (Table 3). We reviewed AEs that led to dose interruption/reductions and did not observe a trend towards any specific AE. Events that led to treatment discontinuation in 10 patients are presented in Supplemental Table 1. Three of these 10 events—cardiac failure, cardiac myopathy and ejection fraction decreased—were considered drug-related.

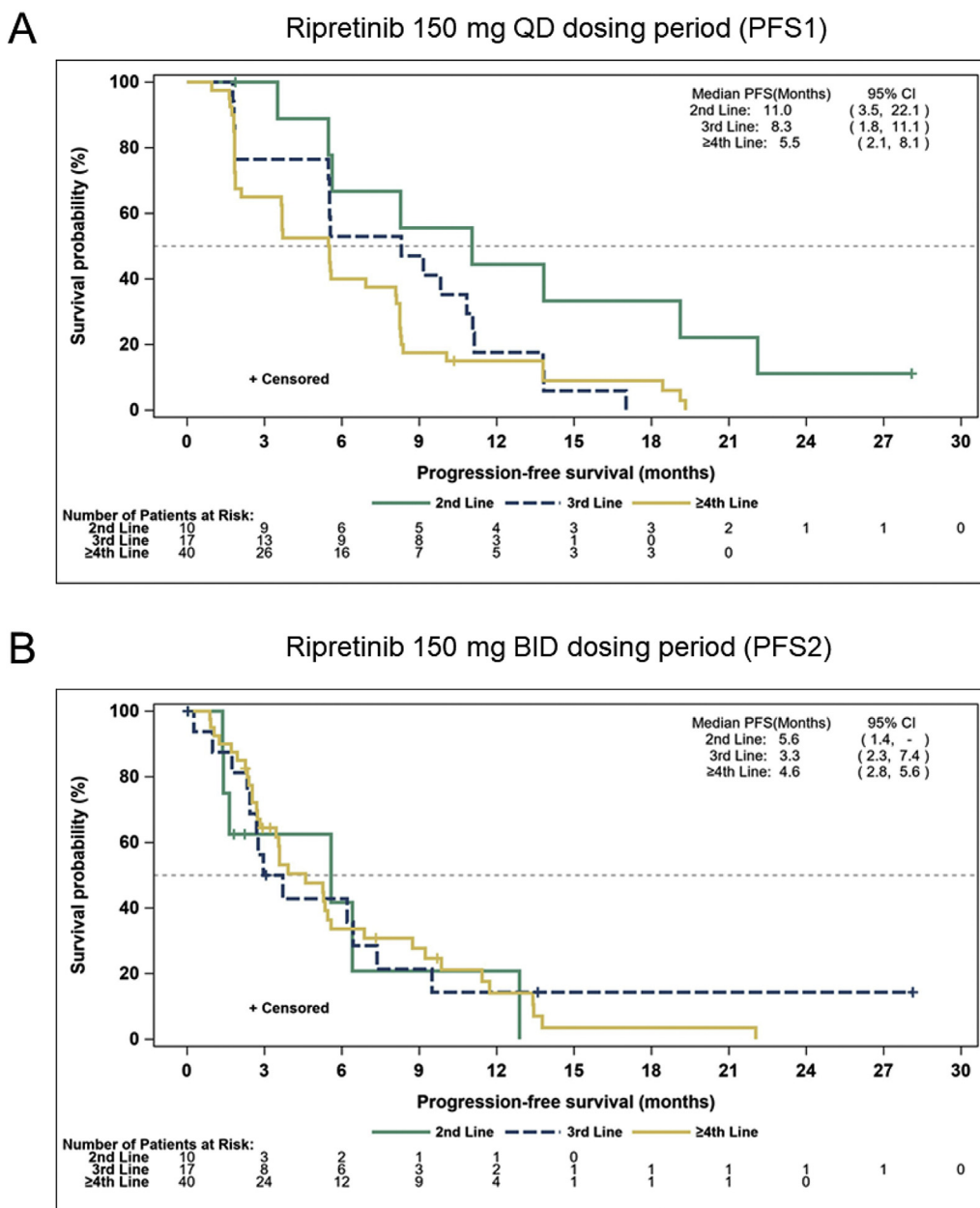


Fig. 1. Kaplan-Meier plot of progression-free survival by the line of therapy in patients with GIST who underwent inpatient dose escalation. BID, twice daily; CI, confidence interval; GIST, gastrointestinal stromal tumour; PFS, progression-free survival; QD, once daily; -, not estimable.

4. Discussion

In the primary report of this phase I trial, ripretinib demonstrated promising efficacy at a range of doses in patients with advanced GIST [14]. The MTD was not reached, and initial PK analysis determined peak plasma concentration (mean C_{max} [coefficient of variation %]) after a single dose of 150 mg ripretinib on cycle 1 day 1 to be 502 ng/mL (56.8%), and exposure (AUC_{0-24h}) was 6634 ng x h/mL (59.8%) [14]. Preclinical pharmacology studies predicted ripretinib 150 mg to be effective, and

thus, combined with the phase I results, 150 mg QD was established as the recommended dose [14].

The present study aimed to determine the efficacy, PK and safety of ripretinib dose escalation after disease progression. Efficacy results of IPDE in patients with GIST demonstrate promising activity across all lines of therapy tested. The mPFS1 by the line of therapy in the IPDE population closely matches the overall mPFS for all patients with GIST enrolled in the phase I study [14]. After disease progression, dose escalation to ripretinib 150 mg BID resulted in additional PFS beyond the

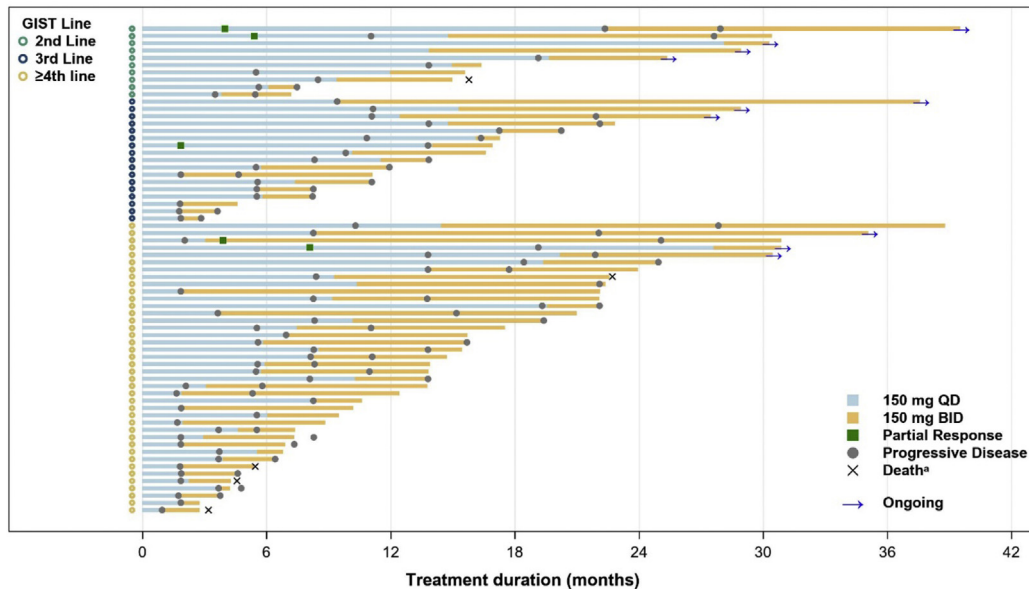


Fig. 2. Total duration of treatment in the GIST inpatient dose escalation population. ^a Deaths noted were those counted as PFS events. BID, twice daily; GIST, gastrointestinal stromal tumour; PFS, progression-free survival; QD, once daily.

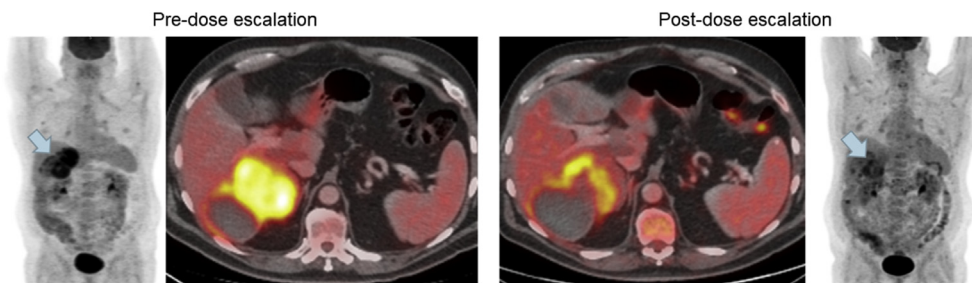


Fig. 3. Radiological images of a partial metabolic response in a patient with GIST who underwent ripretinib inpatient dose escalation. GIST, gastrointestinal stromal tumour.

mPFS1 in these patients by 51%, 40% and 84% for second-, third- and fourth-line or greater therapy, respectively. In addition, an exploratory analysis of metabolic response showed 35.1% of patients had a partial metabolic response on IPDE.

In general, ripretinib 150 mg BID had an acceptable safety profile similar to 150 mg QD, and IPDE resulted in an approximately 2-fold increase in the steady state trough concentration of ripretinib. No new TEAEs were observed with the higher dose. TEAEs leading to dose interruption or dose reduction are comparable during the 150 mg QD period and IPDE period. Ten of 67 (15%) patients discontinued treatment because of TEAEs during the IPDE period, compared with 12 of 142 (8.5%) patients who discontinued treatment because of AEs on ripretinib 150 mg QD [14]. Three cardiac events were observed and considered related to the study drug. Cardiac dysfunction is a safety warning for the 150 mg QD ripretinib regimen, and label precautions indicate that ejection fraction by echocardiogram or multigated acquisition scan should be assessed before

initiating ripretinib and during treatment, as clinically indicated [5].

An IPDE study with TKIs in the treatment of GIST was previously carried out in a large clinical trial of patients with advanced GIST on imatinib as a first-line therapy. After disease progression on imatinib 400 mg QD, 133 patients crossed over to imatinib 400 mg BID, resulting in an mPFS of 81 days. However, the benefit was limited to patients with *KIT* exon 9 primary mutations [15]. Although dose escalation was concluded to be well tolerated, a significant increase in reports of anaemia and fatigue was noted. At 6 months after dose escalation, 17% of patients required a dose reduction and a further 51% discontinued treatment largely as a result of disease progression [15]. Although dose escalation for imatinib is recommended in certain clinical scenarios, specifically, *KIT* exon 9 mutations, this benefit has not been demonstrated for the other TKIs [16].

A limitation of this study is that not all patients who experienced progressive disease received the 150 mg BID

Table 2
TEAEs occurring in >10% of patients with GIST in the 150 mg IPDE period.

Preferred term, n (%)	Ripretinib 150 mg QD period (n = 67)		Ripretinib 150 mg IPDE period ^a (n = 67)	
	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhoea	13 (19.4)	1 (1.5)	19 (28.4)	1 (1.5)
Abdominal pain	15 (22.4)	0	18 (26.9)	7 (10.4)
Nausea	24 (35.8)	0	17 (25.4)	0
Decreased appetite	11 (16.4)	0	16 (23.9)	1 (1.5)
Anaemia	3 (4.5)	0	15 (22.4)	4 (6.0)
Fatigue	23 (34.3)	0	14 (20.9)	2 (3.0)
PPES	24 (35.8)	0	12 (17.9)	0
Alopecia	41 (61.2)	0	11 (16.4)	0
Vomiting	9 (13.4)	0	11 (16.4)	0
Weight decreased	19 (28.4)	0	11 (16.4)	0
Muscle spasms	19 (28.4)	0	10 (14.9)	0
Dyspnoea	5 (7.5)	0	9 (13.4)	2 (3.0)
Back pain	10 (14.9)	0	7 (10.4)	0
Headache	8 (11.9)	0	7 (10.4)	1 (1.5)
Myalgia	33 (49.3)	0	7 (10.4)	0
Oedema peripheral	5 (7.5)	0	7 (10.4)	1 (1.5)
Rash	13 (19.4)	0	7 (10.4)	0

GIST, gastrointestinal stromal tumour; IPDE, inpatient dose escalation; PPES, palmar-plantar erythrodysesthesia syndrome; QD, once daily; TEAE, treatment-emergent adverse event.

^a Only includes TEAEs that are new or worsening.

Table 3
Dose modifications occurring in patients with GIST in the 150 mg IPDE population.

Parameters, n (%)	Ripretinib 150 mg QD period (n = 67)	Ripretinib 150 mg IPDE period (n = 67)
Any TEAE leading to dose interruption	28 (41.8)	30 (44.8)
Any TEAE leading to dose reduction	4 (6.0)	6 (9.0)
Any TEAE leading to treatment discontinuation	N/A	10 (14.9)

GIST, gastrointestinal stromal tumour; IPDE, inpatient dose escalation; N/A, not applicable; QD, once daily; TEAE, treatment-emergent adverse event.

dose (Supplemental Fig. 1). The decision of dose escalation was made by individual investigators based on the patient's best interest. Another limitation is the relatively small sample size across multiple lines of therapy that did not allow for analyses to be stratified by mutational status or to determine whether increased drug exposure led to increased PFS.

5. Conclusions

In conclusion, ripretinib dose escalation (150 mg QD to 150 mg BID) after disease progression was well tolerated and provided additional clinical benefit for patients with advanced GIST. This promising benefit was demonstrated for patients with GIST receiving second-, third-

and fourth-line or greater therapy. Ripretinib IPDE may be a clinically meaningful and well-tolerated strategy for patients with advanced GIST who progress on ripretinib 150 mg QD.

Author contributions

Suzanne George: conceptualisation, resources, supervision, investigation, writing-original draft, and writing-review and editing. **Ping Chi:** resources, supervision, investigation, and writing-review and editing. **Michael C. Heinrich:** resources, supervision, investigation, and writing-review and editing. **Margaret von Mehren:** conceptualisation, resources, supervision, investigation, and writing-review and editing. **Robin L. Jones:** resources, supervision, investigation, and writing-review and editing. **Kristen Ganjoo:** resources, supervision, investigation, and writing-review and editing. **Jonathan Trent:** resources, supervision, investigation, and writing-review and editing. **Hans Gelderblom:** resources, supervision, investigation, and writing-review and editing. **Albiruni Abdul Razak:** resources, supervision, investigation, and writing-review and editing. **Michael S. Gordon:** conceptualisation, resources, supervision, investigation, and writing-review and editing. **Neeta Somaiah:** resources, supervision, investigation, and writing-review and editing. **Julia Jennings:** data curation, visualisation, writing-original draft, and writing-review and editing. **Julie Meade:** visualisation, writing-original draft, and writing-review and editing. **Kelvin Shi:** formal analysis, visualisation, and writing-review and editing. **Ying Su:** visualisation, writing-original draft, and writing-review and editing. **Rodrigo Ruiz-Soto:** conceptualisation, supervision, visualisation, writing-original draft, and writing-review and editing. **Filip Janku:** conceptualisation, data curation, resources, supervision, investigation, writing-original draft, and writing-review and editing.

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Conflict of interest statement

The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: **S.G.** serves in an advisory/consultancy role for AstraZeneca, Bayer, Blueprint Medicines, Daiichi Sankyo, Deciphera Pharmaceuticals, Eli Lilly and Exelixis; has a leadership role in Alliance Foundation; receives licensing royalties from Wolters Kluwer Health and is a shareholder/stockholder of Abbott Laboratories and Allergan, and her institution receives research support from Bayer, Blueprint Medicines, Deciphera Pharmaceuticals, Novartis and Pfizer. **P.C.** serves in an advisory role for Deciphera

Pharmaceuticals, Exelixis and Zailab; has received grant funding from Deciphera Pharmaceuticals, Exelixis, Novartis and Array and has licensing royalties and owns stock in ORIC. **M.C.H.** serves in a consultancy role for Blueprint Medicines, Deciphera Pharmaceuticals and Novartis; receives royalties from Novartis; receives grant funding from Blueprint Medicines and Deciphera Pharmaceuticals and has received travel, accommodations, and expenses from Blueprint Medicines and Deciphera Pharmaceuticals. **M.v.M.** serves in an advisory/consultancy role for Blueprint Medicines, Deciphera Pharmaceuticals and Exelixis and has received travel/accommodation expenses from Deciphera Pharmaceuticals and NCCN, and her institution has received funding from Arog, ASCO, Blueprint Medicines, Deciphera Pharmaceuticals, Gradalis, Genmab, Novartis and Solarius. **R.L.J.** has received honoraria and serves in an advisory role for Adaptimmune Therapeutics, Athenex, Bayer, Boehringer Ingelheim, Blueprint Medicines, Clinigen Group, Daiichi Sankyo, Deciphera Pharmaceuticals, Eisai, Epizyme, Immune Design, Eli Lilly, Merck, PharmaMar, UpToDate; serves in an advisory role for Boehringer Ingelheim and Tracoon and has received funding from MSD. **K.G.** serves in an advisory role for Daiichi Sankyo and Foundation Medicine, and her institution has received grant funding from Deciphera Pharmaceuticals. **J.T.** serves in an advisory/consultancy role for Blueprint Medicines, Deciphera Pharmaceuticals, Daiichi Sankyo, Epizyme and Agios, and his institution has received grant funding from Advenchen, Agios, Blueprint Medicines, Deciphera Pharmaceuticals, and Plexikon. **H.G.** institution has received grant funding from Daiichi Sankyo, Five Prime, Novartis, Deciphera Pharmaceuticals, Eli Lilly, Roche, Eisai, Debio, Boehringer Ingelheim, Pfizer, Amgen and TEVA. **A.A.R.** institution has received grant funding from Deciphera Pharmaceuticals. **M.S.G.** serves in an advisory/consultancy role for Agenus, Daiichi Sankyo, Deciphera Pharmaceuticals, ImaginAB, Imaging Endpoints, RedHill Biopharma, Salarius and Tracoon, and has a leadership role in CareMission; his institution has received grant funding from AbbVie, Aeglea, Agenus, Amgen, Arcus, Astex, BeiGene, Blueprint Medicines, Bristol Meyers Squibb, Calithera, CellDex, Corcept, Clovis, Daiichi Sankyo, Deciphera Pharmaceuticals, Eli Lilly, Endocyte, Five Prime, Fujifilm Pharma, Genocoea, ImaginAB, Medimmune, Merck, Neon, Plexikon, RedHill Biopharma, Revolution Medicine, Roche/Genentech, Salarius, Seattle Genetics, Serono, Syndax, SynDevRx, Tesaro, Tolero, Tracoon, and Veru, and he owns stock in Medelis. **N.S.** serves in an advisory role for Bayer, Blueprint Medicines and Deciphera Pharmaceuticals; has stocks in Pfizer and has received grant funding from Ascentage, AstraZeneca, Daiichi Sankyo, Deciphera Pharmaceuticals, GSK and Karyopharm. **J.J.** is employed by Deciphera Pharmaceuticals. **J.M.** is employed by Deciphera

Pharmaceuticals and owns stock in Deciphera Pharmaceuticals. **K.S.** is employed by Deciphera Pharmaceuticals and owns stock in Alberio, Alnylam, AstraZeneca, Immunogen, Karyopharm, Deciphera Pharmaceuticals, and Spectrum. **Y.S.** is employed by Deciphera Pharmaceuticals. **R.R-S.** is employed by Deciphera Pharmaceuticals and owns stock in Deciphera Pharmaceuticals and Immunogen. **F.J.** serves in an advisory role for Asana, Baush Health, Cardiff Oncology, Deciphera, Guardant Health, Ideaya, IFM Therapeutics, Immunomet, Illumina, Jazz Pharmaceuticals, Novartis, PureTech Health, Sotio and Synlogic and has stocks in Cardiff Oncology, and his institution receives funding from Agios, Asana, Astellas, Astex, Bayer, Bicara, BioMed Valley Discoveries, Biocel, Bristol Myers Squibb, Deciphera, Fujifilm Pharma, Genentech, Ideaya, JS InnoPharm, Eli Lilly, Merck, Novartis, Novellus, Plexikon, Proximagen, Sanofi, Sotio, SpringBank Pharmaceuticals, SQZ Biotechnologies, Synlogic, Synthorx and Symphogen.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejca.2021.07.010>.

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