Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial

Jean-Yves Blay, César Serrano, Michael C Heinrich, John Zalcberg, Sebastian Bauer, Hans Gelderblom, Patrick Schöffski, Robin L Jones, Steven Attia, Gina D'Amato, Ping Chi, Peter Reichardt, Julie Meade, Kelvin Shi, Rodrigo Ruiz-Soto, Suzanne George, Margaret von Mehren

Summary

Background Resistance to approved inhibitors of *KIT* proto-oncogene, receptor tyrosine kinase (*KIT*), and platelet-derived growth factor receptor α (PDGFRA) is a clinical challenge for patients with advanced gastrointestinal stromal tumours. We compared the efficacy and safety of ripretinib, a switch-control tyrosine kinase inhibitor active against a broad spectrum of *KIT* and *PDGFRA* mutations, with placebo in patients with previously treated, advanced gastrointestinal stromal tumours.

Methods In this double-blind, randomised, placebo-controlled, phase 3 study, we enrolled adult patients in 29 specialised hospitals in 12 countries. We included patients aged 18 years or older who had advanced gastrointestinal stromal tumours with progression on at least imatinib, sunitinib, and regorafenib or documented intolerance to any of these treatments despite dose modifications, and who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Eligible patients were randomly assigned (2:1) to receive either oral ripretinib 150 mg once daily (ripretenib group) or placebo once daily (placebo group). Randomisation was done via an interactive response system using randomly permuted block sizes of six and stratified according to number of previous therapies and ECOG performance status. Patients, investigators, research staff, and the sponsor study team were masked to a patient's treatment allocation until the blinded independent central review (BICR) showed progressive disease for the patient. The primary endpoint was progression-free survival, assessed by BICR. The primary analysis was done in the intention-to-treat population and safety was assessed in patients who received at least one dose of study drug. Patients randomly assigned to placebo were permitted to cross over to ripretinib 150 mg at the time of disease progression. The INVICTUS study is registered with ClinicalTrials.gov, number NCT03353753, and with WHO International Clinical Trials Registry Platform, number EUCTR2017-002446-76-ES; follow-up is ongoing.

Findings Between Feb 27, 2018, and Nov 16, 2018, 129 of 154 assessed patients were randomly assigned to receive either ripretinib (n=85) or placebo (n=44). At data cutoff (May 31, 2019), at a median follow-up of 6·3 months (IQR 3·2–8·2) in the ripretinib group and 1·6 months (1·1–2·7) in the placebo group, 51 patients in the ripretinib group and 37 in the placebo group had had progression-free survival events. In the double-blind period, median progression-free survival was 6·3 months (95% CI 4·6–6·9) with ripretinib compared with 1·0 months (0·9–1·7) with placebo (hazard ratio 0·15, 95% CI 0·09–0·25; p<0·0001).The most common (>2%) grade 3 or 4 treatment-related treatment-emergent adverse events in the ripretinib group (n=85) included lipase increase (four [5%]), hypertension (three [4%]), fatigue (two [2%]), and hypophosphataemia (two (2%]); in the placebo group (n=43), the most common (>2%) grade 3 or 4 treatment-related treatment-emergent adverse events were anaemia (three [7%]), fatigue (one [2%]), diarrhoea (one [2%]), decreased appetite (one [2%]), dehydration (one [2%]), hyperkalaemia (one [2%]), acute kidney injury (one [2%]), and pulmonary oedema (one [2%]). Treatment-related serious adverse events were reported in eight (9%) of 85 patients who received ripretinib and three (7%) of 43 patients who received placebo. Treatment-related deaths occurred in one patient in the placebo group (septic shock and pulmonary oedema) and one patient in the ripretinib group (cause of death unknown; the patient died during sleep).

Interpretation Ripretinib significantly improved median progression-free survival compared with placebo and had an acceptable safety profile in patients with advanced gastrointestinal stromal tumours who were resistant to approved treatments.

Funding Deciphera Pharmaceuticals.

Introduction

Gastrointestinal stromal tumours most often harbour oncogenic mutations in receptor tyrosine kinase proto-oncogene, receptor tyrosine kinase (*KIT*), or platelet-derived growth factor receptor α (*PDGFRA*).[1,2] Standard treatment for patients with locally advanced

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Department of Medicine, Centre Léon Bérard, Lyon, France (Prof J-Y Blay MD); **Headquarters, Unicancer, Paris, France** (Prof J-Y Blay); **LYRICAN, Lyon, France** (Prof J-Y Blay); **Faculte Lyon Est, Université Claude Bernard, Lyon, France** (Prof J-Y Blay); **Department of Medical Oncology, Vall d'Hebron Institute of Oncology, Barcelona, Spain** (C Serrano MD); **Department of Medicine, Portland VA Health Care System, Portland, OR, USA** (Prof M C Heinrich MD); **OHSU Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA** (Prof M C Heinrich); **Department of Epidemiology and Preventative Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia** (Prof J Zalcberg PhD); **Department of Medical Oncology, Alfred Health, Melbourne, VIC, Australia** (Prof J Zalcberg); **Department of Medical Oncology, West German Cancer Center, University of Duisburg-Essen, Essen, Germany** (S Bauer MD); **German Consortium for Translational Cancer Research (DKTK), Partner Site Essen, Germany** (S Bauer); **Department of Medical Oncology, Leiden University Medical Center, Leiden, Netherlands** (Prof H Gelderblom MD); **Leuven Cancer Institute and Department of General Medical Oncology, University Hospitals Leuven, Leuven, Belgium** (Prof P Schöffski MD); **Sarcoma Unit, The Royal Marsden NHS Foundation Trust, London, UK** (R L Jones MD); **Division of Clinical Studies, The Institute**

of Cancer Research, London, UK (R L Jones); Department of Hematology and Oncology, Mayo Clinic, Jacksonville, FL, USA (S Attia DO); Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL, USA (G D'Amato MD); Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA (P Chi MD); Department of Medicine, Weill Cornell Medicine, New York, NY, USA (P Chi); Department of Oncology, Helios Klinikum Berlin-Buch, Berlin, Germany (P Reichardt MD); Deciphera Pharmaceuticals, Waltham, MA, USA (J Meade MD, K Shi PhD, R Ruiz-Soto MD); Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA (S George MD); and Department of Hematology and Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA (Prof M von Mehren MD)

Correspondence to: Prof Jean-Yves Blay, Department of Medical Oncology, Centre Léon Bérard, Lyon 69008, France
jean-yves.blay@lyon.unicancer.fr

Research in context

Evidence before this study

We searched PubMed for articles published in English between January 1, 2005, and January 1, 2020, using the terms "gastrointestinal stromal tumor" or "GIST" combined with "KIT" or "PDGFRA". Data from studies show that approved TKIs do not fully cover these secondary resistance mutations, leading to suboptimal efficacy results for progression-free survival and overall survival with second-line and third-line therapies. Patients who had disease progression on approved TKIs (ie, imatinib, sunitinib, regorafenib, or avapritinib [avapritinib is only approved for gastrointestinal stromal tumours with *PDGFRA* exon 18 mutations]) had no other approved treatment options, creating a high unmet clinical need.

Added value of this study

Our study results showed efficacy of ripretinib as a fourth or further line therapy in patients with advanced gastrointestinal stromal tumours, in terms of a significant improvement in median progression-free survival compared with the group receiving placebo. To our knowledge, ripretinib is the first agent to show an improvement in progression-free survival of such magnitude and a median overall survival above 15 months in this patient population. Ripretinib was also generally well tolerated and associated with an acceptable safety profile.

Implications of all the available evidence

Our results showed the clinical activity of ripretinib as fourth-line (or further line) therapy in patients with advanced gastrointestinal stromal tumours. In May, 2020, the US Food and Drug Administration approved ripretinib for the treatment of adult patients with advanced gastrointestinal stromal tumours who have received previous treatment with three or more kinase inhibitors, including imatinib.

metastatic gastrointestinal stromal tumours are KIT and PDGFRA-directed tyrosine-kinase inhibitors (TKIs).[3–5] First-line treatment with imatinib for patients with advanced gastrointestinal stromal tumours results in response or tumour control in more than 80% of patients.[2,3] However, approximately 50% of patients with advanced gastrointestinal stromal tumours have progressive disease by 24 months and estimated 10-year progression-free survival is around 9%.[3,6,7] Progressing metastases often harbour secondary mutations in the ATP-binding domain or activation loop of *KIT,* which represent a major mechanism of resistance to TKIs.[8–10] Both sunitinib and regorafenib, approved for second-line (sunitinib) and third-line (regorafenib) treatment for advanced gastrointestinal stromal tumours, inhibit some of these resistance mutations,[11,12] but neither drug covers the full spectrum of possible mutations,[12,13] yielding a median progression-free survival of 5·6 months for sunitinib and 4·8 months for regorafenib.[4,14–16] Avapritinib is only approved for gastrointestinal stromal tumours with *PDGFRA* exon 18 mutations, which account for approximately 6% of the overall population of patients with gastrointestinal stromal tumours.[17–19]

See Online for appendix

Ripretinib (DCC-2618) is a switch-control TKI that broadly inhibits KIT and PDGFRA kinase signalling through a dual mechanism of action.[20] Ripretinib specifically and durably binds to both the switch pocket and the activation loop to lock the kinase in the inactive state, preventing downstream signalling and cell proliferation. This dual mechanism of action provides broad inhibition of *KIT* and PDGFRA kinase activity, including for wild-type *KIT* and *PDGFRA* mutations and multiple primary and secondary mutations associated with drug-resistant gastrointestinal stromal tumours.

In in-vitro enzyme assays, ripretinib inhibited platelet-derived growth factor receptor β (PDGFRB), angiopoietin-1 receptor (TIE2), vascular endothelial growth factor receptor 2 (VEGFR2), and serine and threonine-protein kinase B-raf (*BRAF*), among other kinases.[20]

A first-in-human, phase 1 study in patients with gastrointestinal stromal tumours or other advanced solid tumours determined the recommended phase 2 dose of ripretinib as 150 mg once daily, which was associated with a favourable tolerability profile and was active in patients with advanced gastrointestinal stromal tumours that were refractory to multiple previous TKIs. Notably, doses of ripretinib 150 mg twice daily were well tolerated without clinically meaningful dose-limiting side-effects.[21] In this phase 3 INVICTUS study, we aimed to evaluate the safety and efficacy of ripretinib as fourth-line therapy (or further-line therapy) versus placebo in patients with advanced gastrointestinal stromal tumours.

Methods

Study design and participants

INVICTUS is a double-blind, randomised, placebo-controlled, phase 3 study done at 29 specialised hospitals in 12 countries across North America, Europe, and Asia (appendix p 1).

Key inclusion criteria were patients aged 18 years or older with a diagnosis of gastrointestinal stromal tumour with at least one measurable lesion according to modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST 1.1). The mRECIST modifications followed those described by Demetri and colleagues,[15] and included the following changes: lymph nodes were not chosen as target lesions, enlarged lymph nodes were followed up as non-target lesions, bone lesions were not chosen as target lesions, and PET was not acceptable for radiological evaluation. A progressively growing new tumour nodule within a pre-existing tumour mass had to meet the following criteria to be considered as unequivocal evidence of progression according to mRECIST 1.1: the lesion was at least 2 cm in size and definitively a new

active gastrointestinal stromal tumour lesion (eg, the lesion could show enhancement with contrast or other criteria to rule out artifact) or the lesion had to be expanding on at least two sequential imaging studies. An archival tumour tissue sample was provided if no anticancer therapy had been administered after sample collection; otherwise, a fresh tumour tissue sample was required before the first dose of study drug. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, had adequate organ function and bone marrow reserve, and had progressed on at least imatinib, sunitinib, and regorafenib, or had documented intolerance to any of these treatments despite dose modifications; progression or intolerance was determined by the investigator. Key exclusion criteria included anticancer therapy received within 14 days or five times the half-life (whichever was longer) before the first dose of study drug. After study commencement, our eligibility criteria was expanded to include patients with *KIT* and *PDGFRA* wild-type gastrointestinal stromal tumours. Complete inclusion and exclusion criteria are available in the study protocol, which is available online.

This study was done in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice. Patients had to provide written, informed consent to participate in this study. The protocol, protocol amendments, and informed-consent documents were approved by the institutional review board or ethics committee at each site before the start of the study.

Randomisation and masking

Patients were randomly assigned (2:1) to receive either ripretinib or matching placebo tablets. Randomisation was done via an interactive response technology system by use of randomly permuted block sizes of six and stratified according to number of previous therapies (three *vs* four or more) and ECOG performance status (0 *vs* 1 or 2); the proportion of enrolled patients who had received four or more therapies was limited to less than 40%. The treatment allocation sequence was generated with a computer system, whereby concealment of the allocation was done by the interactive response technology. Patients, investigators, research staff, and the sponsor study team were masked to a patient's treatment allocation until the blinded independent central review (BICR) confirmed progressive disease for the patient.

At the time of progressive disease by BICR (as defined by mRECIST version 1.1), patients were unblinded and offered the option to continue or crossover to ripretinib open-label therapy.

Procedures

Patients were assigned to receive either oral ripretinib 150 mg once a day plus best supportive care or matching placebo once a day plus best supportive care, for 28-day cycles (appendix p 3). Patients received their assigned treatment until they developed progressive disease, experienced unacceptable toxic effects, or withdrew consent. At the time of progressive disease, patients who received ripretinib were permitted to dose escalate to ripretinib 150 mg twice a day, continue ripretinib 150 mg once a day if showing clinical benefit, or discontinue ripretinib; patients who received placebo were permitted to cross over to ripretinib 150 mg once a day or discontinue the study. Patients who crossed over to ripretinib from placebo and had further progressive disease (determined by investigator assessment) were permitted to dose escalate to ripretinib 150 mg twice a day, continue ripretinib 150 mg once a day if showing clinical benefit, or discontinue study therapy. Study drug dose interruptions or modifications were permitted at the discretion of the investigator. In the double-blind period, the first dose reduction was to 100 mg once a day and the second reduction was to 50 mg once a day. Patients requiring a dose lower than 50 mg once a day were discontinued from the study.

Tumour assessments using CT scans (MRI scans were permitted for patients allergic to contrast media) were made at screening, then every cycle (for 4 weeks) through cycle 4. After cycle 4 (or if the patient was found to be on ripretinib once they were unblinded), assessments were done every other cycle. If a patient crossed over from placebo to ripretinib, tumour assessments were done every other cycle, and again at the end of treatment. During the double-blind period, tumour assessments were done on the basis of BICR. An initial indication of a partial response or complete response based on the BICR was confirmed 4 or more weeks later. During the open-label period, overall response based on investigator assessments was used to guide treatment options. An initial indication of a partial response or complete response based on investigator assessment was confirmed 4 or more weeks later. Patients were contacted every 3 months by phone to collect long-term overall survival data.

For the **study protocol** see http://link.deciphera.com/INVsp

Safety and tolerability were assessed by analysis of clinical laboratory tests, ECOG performance status, and changes in vital signs and weight at screening, and were assessed on cycle 1 day 1 (baseline), cycle 1 day 15, day 1 of each subsequent cycle, and at the end of treatment. 12-lead electrocardiogram (ECG) was done at screening, cycle 1 day 1 (baseline), day 1 of each subsequent cycle, and at the end of treatment. Left ventricular ejection fraction was based on echocardiogram or multigated acquisition scan and dermatological examination by a consulting dermatologist at screening, cycle three on day 1, and every third cycle thereafter, and at the end of treatment. Physical examinations were done at screening and then driven by clinical findings and patient complaints. Adverse events were monitored continuously from the signing of informed consent to safety follow-up (30 days after the last dose). Severity of adverse events were rated by investigators according to the National Cancer Institute Common

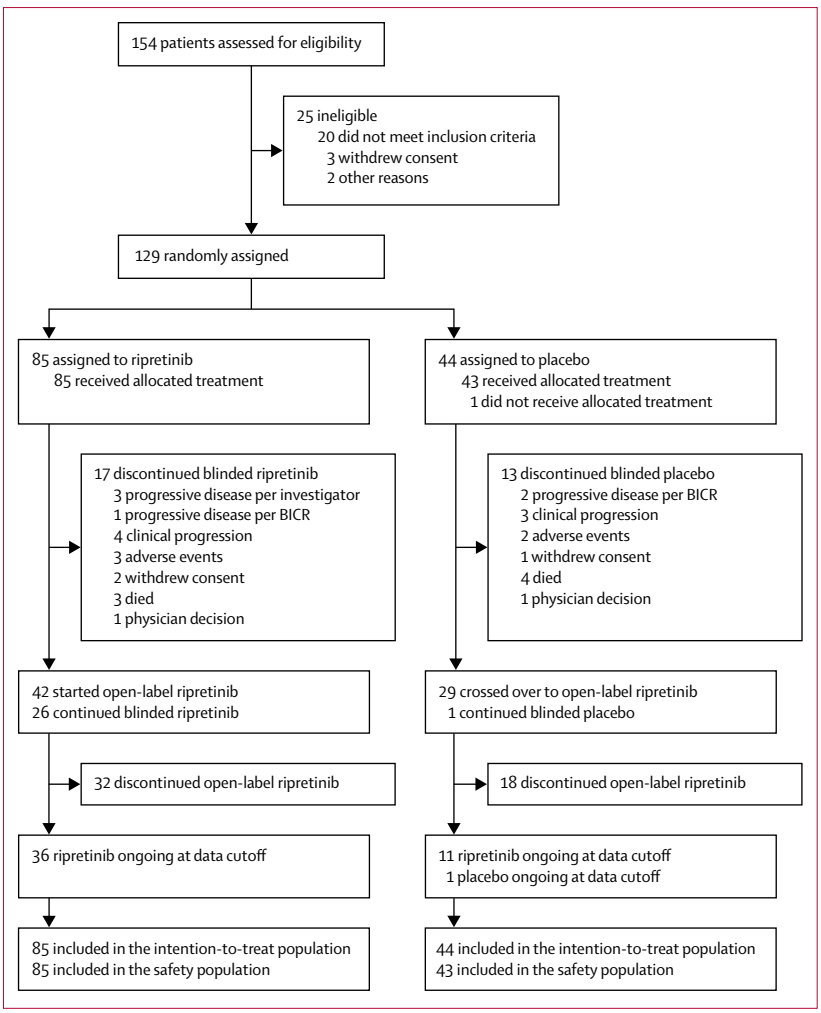

Figure 1: **Trial profile**
Data reported as of the cutoff date for the primary completion date (May 31, 2019) are shown. BICR=blinded independent central review.

Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Safety evaluations included the occurrence of treatment-related treatment-emergent adverse events and treatment-related serious adverse events, as well as treatment-related dose reductions, interruptions, or discontinuations of study drug.

Select quality of life (QOL) assessments that were prespecified in the statistical analysis plan were done on cycle 1 day 1 (baseline), cycle 1 day 15, day 1 of each subsequent cycle, and at end the of treatment using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer 30-item (EORTC QLQ-C30) questionnaire (physical and role functioning questions only) and the EuroQol 5-Dimension 5-Level (EQ-5D-5L) EuroQol visual analogue scale (EQ-VAS). The EORTC QLQ-C30 physical function score was calculated from questions that asked if patients had trouble doing strenuous activities like carrying a heavy shopping bag or suitcase, trouble taking a short or long walk, if they needed to stay in bed or a chair during the day, and if they needed help with eating, dressing, washing, or using the toilet. The role function score was calculated from questions that asked if there were any limitations in daily activities or the pursuit of hobbies or other leisure activities. Patients scored each question on a scale of 1–4, in which 1 was "Not at all" and 4 was "very much". The EQ-VAS asked patients to report their overall health on a vertical visual analogue scale, ranging from "Worst Possible" to "Best Possible" health. These three scores were converted to a number ranging from 0 to 100.

Outcomes

The primary efficacy endpoint was progression-free survival (the interval between the date of randomisation to the date of documented progressive disease or death due to any cause) according to mRECIST 1.1, as assessed by BICR. The key secondary efficacy endpoint was objective response rate (confirmed complete response and partial response assessed by BICR).

Other secondary endpoints were overall survival (the interval between the date of randomisation and the date of death from any cause), time to progression (the interval between the date of randomisation and the earliest documented evidence of progressive disease based on independent radiological review), time to best response, progression-free survival by investigator assessment (the interval between the date of randomisation and the earliest documented evidence of progressive disease based on investigator evaluation or death from any cause), QOL, and safety. Other secondary endpoints were disease control rate (patients who had a complete response, partial response, or stable disease) at 12 weeks, and pharmacokinetic or pharmacodynamic analyses. Disease control rate is not reported because it was not analysed, and pharmacokinetic and pharmacodynamic results will be reported separately.

Statistical analysis

A sample size of 120 patients (ripretinib, n=80; placebo, n=40) was calculated to provide both power for efficacy and size for the safety database with an assumed 15% patient dropout, and a two-sided 0·05 significance level in testing the hypothesis of no difference between ripretinib and placebo was expected to provide over 90% power to detect a difference in progression-free survival between ripretinib and placebo. This power assumed a median progression-free survival of 4·5 months for ripretinib and 1·0 month for placebo and approximately 80% power to detect a 20% difference in objective response, with the assumption of an objective response for ripretinib of 22% and 2% for placebo. To control family-wise type I error, the hypothesis tests for treatment differences were done at a two-sided 0·05 level of significance sequentially in the following order: progression-free survival, objective response rate, overall survival, and QOL as determined by changes

from baseline to cycle two on day 1 in physical and role functioning scale subsets of the EORTC-QLQ-C30 (each at 0·025 level of significance). Other endpoints (eg, time to progression, time to best response, and investigator assessed progression-free survival) were not included in the hierarchy because we deemed that there would be insufficient power to test these. Once a hypothesis test was non-significant at α=0·05 level, the remaining analyses were reported as descriptive.

Results of study endpoints are described herein for the double-blind period with the exception of overall survival and disposition, which reflect data from both the double-blind and open-label periods. The decision to report the double-blind and open-label periods separately was made post hoc.

Time-to-event data (progression-free survival, overall survival, time to progression, and time to best response) were summarised using the Kaplan-Meier method and associated two-sided 95% CI. We used a two-sided stratified log-rank test (0·05 significance level) to evaluate treatment difference. Hazard ratios (HRs) were obtained from a Cox regression model, and the 95% CIs were obtained using the Wald method. The proportional hazards assumption was examined by visual inspection of the log (-log) plot (appendix p 4). Objective response was analysed by an unstratified two-sided Fisher's exact test (using a 0·05 significance level) to evaluate treatment difference, and the 95% CI of the treatment difference was calculated with the Newcombe method.

Descriptive statistics were used to summarise safety data and QOL variables. For the EQ-VAS, a t-test was done between the ripretinib and placebo groups to evaluate changes in scores from baseline to cycle 2 day 1. For the questions from the EORTC QLQ-C30, analysis of covariance models were built to assess for change from baseline to cycle 2 day 1. Fixed effects were treatment, ECOG performance status at baseline, and the number of previous treatments. A patient was excluded from the analyses if data from baseline or cycle 2 day 1 were missing. Minimally important clinical differences have not been established for gastrointestinal stromal tumours. The minimally important clinical difference for health-related QOL is often found to be near 0·3 times standard deviation of the baseline value, which was used as an estimate.[22,23] Subgroup analyses of progression-free survival were prespecified in the statistical analysis plan that was finalised before database lock and unblinding of the study. In each subgroup, the HR was from Cox regression with treatment as a fixed factor and the 95% CI of the HR was based on the Wald method. The subgroup analysis of overall survival on crossover was post-hoc. The survival curves and median overall survival of the subgroups are based on the Kaplan-Meier method.

The intention-to-treat population, defined as all patients who provided informed consent and were randomised, was used for all efficacy analyses. The safety population was defined as all patients who received at least one dose of study drug. An independent data monitoring committee reviewed safety data periodically throughout the course of this study.

More detailed statistical methods are described in the study protocol. Statistical analyses were done with SAS (version 9.4).

	Ripretinib group (n=85)	Placebo group (n=44)
Median age, years	59 (29–82)	65 (33–83)
18–64	57 (67%)	22 (50%)
65–74	20 (24%)	12 (27%)
≥75	8 (9%)	10 (23%)
Sex		
Male	47 (55%)	26 (59%)
Female	38 (45%)	18 (41%)
Race		
White	64 (75%)	33 (75%)
Non-white	13 (15%)	7 (16%)
Not reported	8 (9%)	4 (9%)
Region		
USA	40 (47%)	20 (46%)
Non-USA	45 (53%)	24 (55%)
Number of previous therapies		
3	54 (64%)	27 (61%)
4–7	31 (36%)	17 (39%)
ECOG performance status		
0	37 (44%)	17 (39%)
1 or 2	48 (56%)	27 (61%)
Primary tumour site		
Gastric	40 (47%)	18 (41%)
Jejunum or ileum	20 (24%)	8 (18%)
Mesenteric or omental	6 (7%)	6 (14%)
Other	7 (8%)	4 (9%)
Duodenum	2 (2%)	8 (18%)
Colon or rectum	9 (11%)	0
Unknown	1 (1%)	0
Sum of longest diameters of target lesions (mm), median (range)*	123 (28–495)	142 (17–412)
Primary mutation (central testing of tumour tissue)		
KIT exon 9	14 (17%)	6 (14%)
KIT exon 11	47 (55%)	28 (64%)
Other *KIT*	2 (2%)	2 (5%)
PDGFRA	3 (4%)	0
KIT and *PDGFRA* wild-type	7 (8%)	3 (7%)
Not available† or not done‡	12 (14%)	5 (11%)

Data are median (IQR), n (%), or median (range), and percentages might not add up to 100 due to rounding. ECOG=Eastern Cooperative Oncology Group. *KIT*=KIT proto-oncogene, receptor tyrosine kinase. *PDGFRA*=platelet-derived growth factor receptor α. *Independent assessment. †Tumour tissue analysed for baseline mutations but analysis failed. ‡Biopsy completed per protocol but sample not received for analysis.

Table 1: **Baseline patient characteristics**

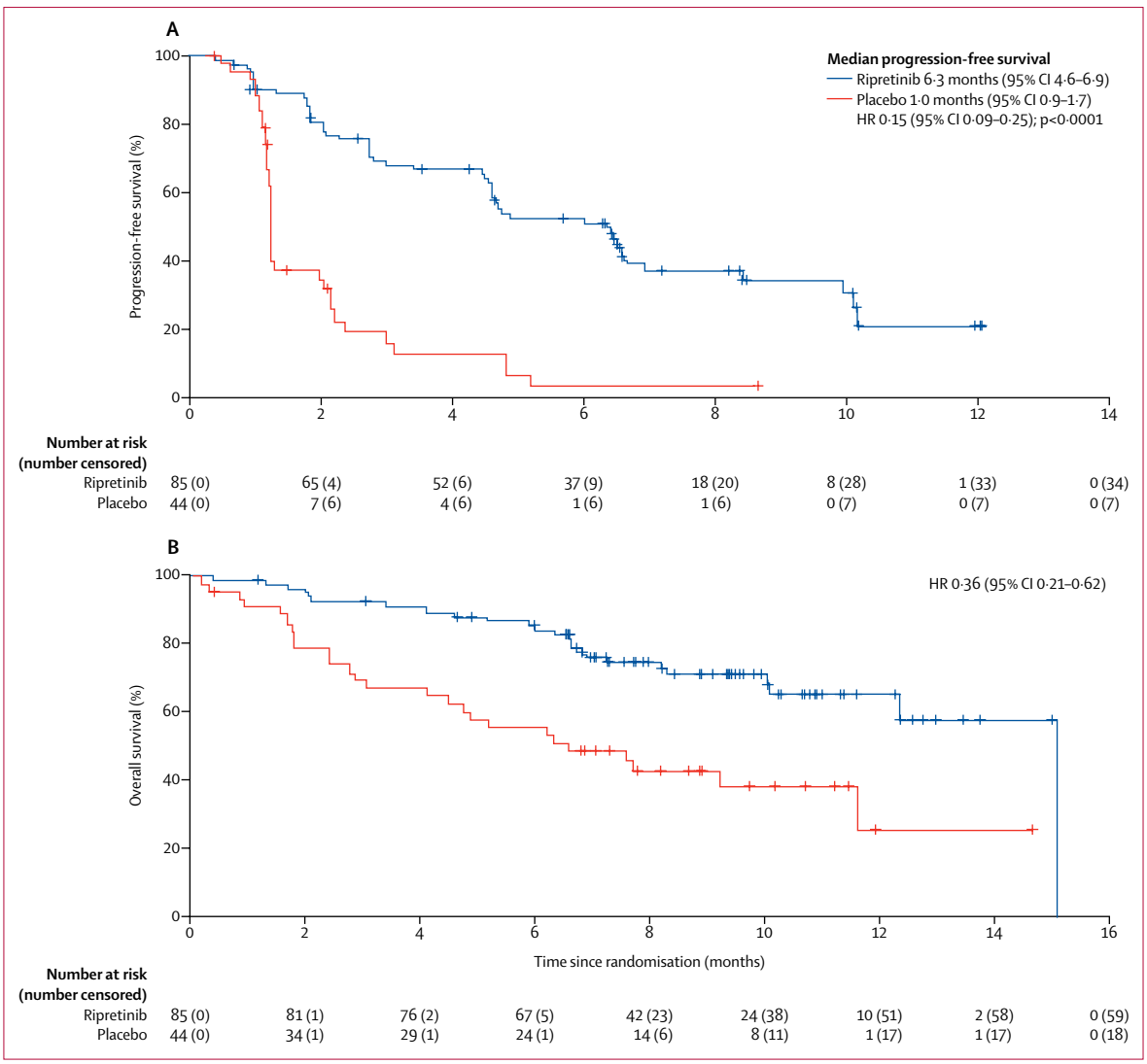

Figure 2: **Kaplan-Meier survival curves**
(A) Progression-free survival by blinded independent central review in patients receiving ripretinib or placebo in the double-blind part of the study. Crosses denote censoring events. (B) Overall survival in patients receiving ripretinib or placebo in the double-blind and open-label periods. Owing to the hierarchical testing procedures of the endpoints, overall survival endpoint could not be formally tested because the objective response rate was not statistically significant.

This clinical trial is registered with ClinicalTrials.gov, number NCT03353753, and with the World Health Organization International Clinical Trials Registry Platform, number EUCTR2017-002446-76-ES. Follow-up is ongoing.

Role of the funding source

This study was designed by the funder (Deciphera Pharmaceuticals) with input from the investigators. Data collected by the investigators were analysed by Deciphera Pharmaceuticals, and interpreted jointly with all the authors. The authors had access to the data to verify the completeness and accuracy of the data reported and for the adherence of the study to the protocol and the statistical analysis plan. The manuscript was written by J-YB and MvM with medical writing assistance provided by the sponsor. The corresponding author had full access to all the data in this study and had final responsibility for the decision to submit for publication.

Results

Between Feb 27, 2018 and Nov 16, 2018, 154 patients were assessed for eligibility, of whom 129 were randomly assigned to either the ripretinib group (n=85) or the placebo group (n=44; figure 1). Baseline characteristics are in table 1. At the data cutoff (May 31, 2019), the median follow-up time in the double-blind period was 6·3 months (IQR 3·2–8·2) for the ripretinib group and 1·6 months (1·1–2·7) for the placebo group. The median

relative dose intensity in the double-blind period was 100% (IQR 98·1–100·0) for the ripretinib group and 97% (86·5–100·0) for the placebo group. 15 patients did not cross over to ripretinib from the placebo group (figure 1).

Median progression-free survival by BICR was 6·3 months (95% CI 4·6–6·9) for ripretinib versus 1·0 months (0·9–1·7) for placebo (HR 0·15, 95% CI 0·09–0·25; p<0·0001; figure 2A). 51 (60%) of 85 patients receiving ripretinib and 37 (84%) of 44 patients receiving placebo had progression or died. Progression-free survival at 6 months were estimated to be 51% (39·4–61·4) for ripretinib and 3·2% (0·2–13·8) for placebo. Progression-free survival analyses across assessed patient subgroups are shown in the appendix (p 4). This analysis of progression-free survival by subgroup was prespecified in the statistical analysis plan and is described for inclusion on p 5. Median progression-free survival (as per investigator assessment) was 4·7 months (95% CI 4·2–8·2) in the ripretinib group and 1·0 months (0·9–1·4) in the placebo group (HR 0·19, 95% CI 0·12–0·32). Overall discordance was observed in 26 (20%) of 129 patients; the investigator assessed progressive disease and BICR assessed non-progressive disease in nine (7%) of 129 patients, and the investigator assessed non-progressive disease and the BICR assessed progressive disease in 17 (13%) of 129 patients.

In the ripretinib group, eight (9·4%, 95% CI 4·2–17·7) of 85 patients had a confirmed objective response, all of whom had partial responses as assessed by BICR. None of the patients who received placebo had a confirmed objective response (table 2). As of data cutoff, the median duration of response had not yet been reached, and one of eight responders had progressed (figure 3). Median time to best response was 1·9 months (IQR 1·0–2·7). Median time to progression was 6·4 months (95% CI 4·6–8·4) in the ripretinib group and 1·0 month (0·9–1·7) in the placebo group.

Median overall survival was 15·1 months (95% CI 12·3–15·1) in the ripretinib group and 6·6 months (4·1–11·6) in the placebo group (HR 0·36, 95% CI 0·21–0·62; figure 2B), inclusive of the double-blind and open-label periods. 26 (31%) of 85 patients who received ripretinib and 26 (59%) of 44 patients who received placebo had died by the data cutoff. At 6 months, estimated overall survival was 84·3% (95% CI 74·5–90·6) for ripretinib and 55·9% (39·9–69·2) for placebo. At 12 months, estimated overall survival was 65·4% (51·6–76·1) for the ripretinib group and 25·9% (7·2–49·9) for the placebo group. Owing to the hierarchal testing procedure of the endpoints, overall survival could not be formally tested for statistical significance because the objective response was not significant. Overall survival in patients who crossed over to the ripretinib group from the placebo group compared with those who did not cross over is shown in the appendix (p 5). This analysis of overall survival by crossover group was post hoc and is described for inclusion on p 5.

	Ripretinib group (n=85)	Placebo group (n=44)	p value
Confirmed objective response	8 (9%; 4–18)	0 (0%; 0–8)	0·0504
Complete response	0 (0%; 0–4)	0 (0%; 0–8)	..
Partial response	8 (9%; 4–18)	0 (0%; 0–8)	..
Stable disease (6 weeks)	56 (66%; 55–76)	9 (20%; 10–35)	..
Stable disease (12 weeks)	40 (47%; 36–58)	2 (5%; 1–16)	..
Progressive disease	16 (19%; 11–29)	28 (64%; 48–78)	..
Not evaluable	4 (5%)	3 (7%)	..
No response assessment	1 (1%)	4 (9%)	..

Data are n (%; 95% CI) or n (%). *Assessed by blinded independent central review.

Table 2: **Objective response rate***

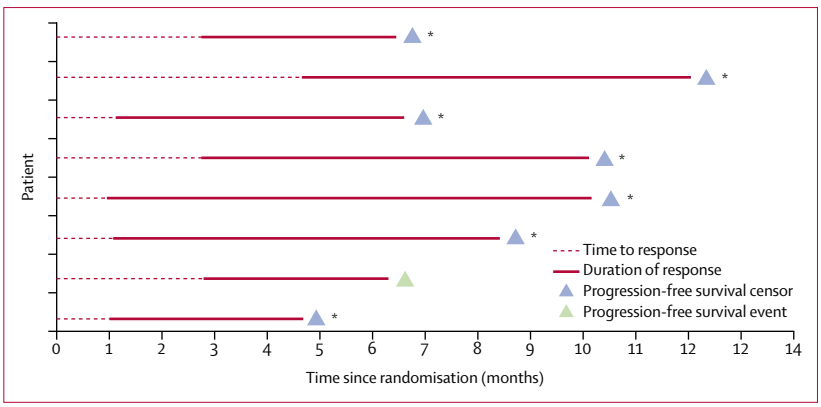

Figure 3: **Time to response and duration of response in the eight patients in the ripretinib group who responded**

As of data cutoff, the median duration of response has not been reached and only one of eight responders had disease progression. *Patient responding at time of data cutoff.

The most common (occurring in ≥20% of patients in the ripretinib group) treatment-related treatment-emergent adverse events in patients receiving ripretinib were alopecia, myalgia, nausea, fatigue, palmar–plantar erythrodysesthesia (also known as hand–foot syndrome), and diarrhoea (table 3). Palmar–plantar erythrodysesthesia occurred exclusively in patients treated with ripretinib and all events were grade 1 (11 [13%] of 85 patients) or grade 2 (seven [8%] patients). The most common (>2%) grade 3 or 4 treatment-related treatment-emergent adverse events in the ripretinib group were lipase increase (four [5%] of 85 patients), hypertension (three [4%]), fatigue (two [2%]), and hypophosphataemia (two (2%]). In the placebo group, the most common (>2%) grade 3 or 4 treatment-related treatment-emergent adverse events were anaemia (three [7%] of 43 patients), fatigue (one [2%]), diarrhoea (one [2%]), decreased appetite (one [2%]), dehydration (one [2%]), hyperkalaemia (one [2%]), acute kidney injury (one [2%]), and pulmonary oedema (one [2%]; table 3). Treatment-related serious adverse events were reported in eight (9%) of

	Ripretinib group (n=85)				Placebo group (n=43)*			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Alopecia	42 (49%)†	..	..	..	1 (2%)	..	..	..
Myalgia	23 (27%)	1 (1%)	..	..	4 (9%)	0	..	..
Nausea	21 (25%)	1 (1%)	..	..	1 (2%)	0	..	..
Fatigue	20 (24%)	2 (2%)	..	..	6 (14%)	1 (2%)	..	..
Palmar–plantar erythrodysesthesia syndrome	18 (21%)	0	..	..	0	0	..	..
Diarrhoea	17 (20%)	1 (1%)	0	0	2 (5%)	1 (2%)	0	0
Constipation	13 (15%)	0	0	0	3 (7%)	0	0	0
Decreased appetite	12 (14%)	1 (1%)	0	0	2 (5%)	1 (2%)	0	0
Weight loss	13 (15%)	0	..	..	3 (7%)	0	..	..
Blood bilirubin increased	12 (14%)	0	0	..	0	0	0	..
Arthralgia	10 (12%)	0	..	..	0	0	..	..
Muscle spasms	10 (12%)	0	..	..	2 (5%)	0	..	..
Hypertension	4 (5%)	3 (4%)	0	0	1 (2%)	0	0	0
Lipase increase	4 (5%)	4 (5%)	0	..	0	0	0	..
Pain in extremity	5 (6%)	1 (1%)	..	..	1 (2%)	0	..	..
Hypophosphataemia	3 (4%)	2 (2%)	0	0	0	0	0	0
Anaemia	2 (2%)	0	1 (1%)	0	1 (2%)	2 (5%)	1 (2%)	0
Blood triglycerides increase	1 (1%)	1 (1%)	0	0	0	0	0	0
Dermatosis	1 (1%)	1 (1%)	0	0	0	0	0	0
Dehydration	1 (1%)	0	0	0	0	1 (2%)	0	0
Gastroesophageal reflux disease	1 (1%)	1 (1%)	..	..	0	0	..	..
Hyperkalaemia	0	1 (1%)	0	0	0	1 (2%)	0	0
Hypokalaemia	0	1 (1%)	0	0	0	0	0	0
Anal abscess	0	1 (1%)	0	0	0	0	0	0
Ascites	0	1 (1%)	0	0	0	0	0	0
Cardiac failure	0	1 (1%)	0	0	0	0	0	0
Death, reason unknown	..	..	..	1 (1%)	..	..	..	0
Fecaloma	0	1 (1%)	0	0	0	0	0	0
Skin infection	0	1 (1%)	0	0	0	0	0	0
Syncope	..	1 (1%)	..	..	..	0	..	..
Upper gastrointestinal haemorrhage	0	1 (1%)	0	0	0	0	0	0
Acute kidney injury	0	0	0	0	0	1 (2%)	0	0
Pulmonary oedema	0	0	0	0	0	0	1 (2%)	0
Septic shock	..	..	0	0	..	..	0	1 (2%)

Data are n (%). Treatment-related treatment-emergent adverse events are listed that occurred in ≥10% of patients in either treatment group or were reported as grade 3, 4, or 5 in either treatment group are shown. .. indicates that no data were captured per adverse event grade ratings specified by Common Terminology Criteria for Adverse Events version 4.03. *44 patients were randomly assigned to receive placebo, but one patient did not receive treatment. †24 (63%) of 38 women who were given ripretinib had alopecia.

Table 3: **Treatment-related treatment-emergent adverse events**

85 patients who received ripretinib (one each of the following: anaemia, cardiac failure, death of unknown cause, dyspnoea, fecaloma, gastro-oesophageal reflux disease, hyperkalaemia, hypophosphataemia, nausea, and upper gastrointestinal haemorrhage; some patients might have experienced more than one event) and three (7%) of 43 patients who received placebo (one each of the following: hyperkalaemia, dehydration, pulmonary oedema, and septic shock; some patients might have experienced more than one event).

Treatment-related treatment-emergent adverse events leading to a dose reduction were reported in five (6%) of 85 patients in the group who received ripretinib and one (2%) of 43 patients who received placebo (appendix p 2). Treatment-related treatment-emergent adverse events leading to study treatment discontinuation were reported in four (5%) of 85 patients in the ripretinib group (due to cardiac failure, death of unknown cause, general physical health deterioration, and palmar–plantar erythrodysesthesia) and one (2%) of 43 patients who received placebo (due to fatigue; appendix p 2). 12 (14%) of 85 patients in the ripretinib group died (11 deaths due to disease progression and one death due to unknown reason) and 13 (30%) of 43 patients in the placebo group died (11 deaths due to

disease progression and two deaths due to an adverse event [one acute kidney injury and one septic shock]). One treatment-related death was recorded in the placebo group (due to septic shock and pulmonary oedema) and one treatment-related death was recorded in the ripretinib group (cause unknown; the patient died during sleep).

Compliance with completion of questionnaires for quality of life is shown in the appendix (p 2). Role and physical functioning (as assessed by EORTC-QLQ-C30) from baseline to cycle 2 day 1 remained stable in the ripretinib group with adjusted mean change in score of 3·5 (95% CI −3·4 to 10·5) for role functioning and 1·6 (−2·5 to 5·7) for physical functioning, compared with a decrease with placebo of 17·1 for role functioning (95% CI −27·0 to −7·1) and a decrease of 8·9 for physical functioning (−14·8 to −3·0; appendix p 2). Overall health (as assessed by EQ-VAS) from baseline to cycle 2 on day 1 also remained stable in the ripretinib group with adjusted mean change in scores of 3·7 (95% CI −1·1 to −8·6) compared with a decrease in the group that received placebo of 8·9 (−15·9 to −1·9). Using either QOL instrument, the results showed a clinically relevant difference between ripretinib and placebo. Owing to hierarchal testing procedures of the endpoints, the QOL endpoint could not be formally tested for statistical significance.

Discussion

Results of the INVICTUS study showed that ripretinib as fourth-line (or further line) therapy for patients with advanced gastrointestinal stromal tumours significantly improved median progression-free survival compared with placebo. Patients were stratified by ECOG performance status and number of previous therapies, which are known prognostic variables. The difference in the objective response rate between the groups was not significant; however, the median overall survival seemed to be increased in the ripretinib group, which is clinically relevant in this patient population. Furthermore, ripretinib had a favourable safety profile and showed clinically meaningful maintenance of role and physical function and health status compared with placebo.

The median progression-free survival in the ripretinib group was 6·3 months and the objective response rate was 9%. Historically, the median progression-free survival was 5·6 months (objective response 6·8%) for second-line sunitinib, 4·8 months (objective response 4·5%) for third-line regorafenib, 1·8 months (objective response 0%) for third-line (or further line) imatinib (rechallenge after failure of imatinib), and 3·4 months (objective response; 0%) for third-line (or further line) pazopanib.[4,15,16,24,25] Responses in patients treated with ripretinib were durable, with the median duration of response not yet reached; one of eight responders had progressive disease at the time of data cutoff. Additionally, more patients receiving ripretinib had stable disease for 12 weeks and fewer had progressive disease than patients who received placebo. The large percentage of patients who received ripretinib with stable disease is notable as the absence of progression is considered an important marker of therapeutic benefit in patients who have gastrointestinal stromal tumours.[26,27] Unlike some other advanced solid tumours, the absence of progression (whether a partial response or stable disease) is predictive of progression-free survival and overall survival benefit in patients with advanced gastrointestinal stromal tumours.[27] The key secondary endpoint of objective response in the ripretinib group did not meet our predefined assumption of 22%. This estimated assumption was for the purpose of a power calculation in the study design. Our results, despite not meeting the predefined objective response assumption, support the outlook that treatment of patients with advanced gastrointestinal stromal tumours is more about control of the disease rather than response according to mRECIST 1.1 criteria.

In clinical oncology trials, overall survival is considered to be the gold standard for showing clinical benefit, because it provides a direct benefit to patients and is not subject to investigator interpretation. Ripretinib increased the median overall survival over placebo in both the double-blind and open-label periods. Notably, 29 (66%) of 44 patients in the placebo group crossed over to ripretinib at time of progression, and thus the improvement in overall survival could potentially be underestimated. 15 (34%) of 44 patients did not cross over to the ripretinib group, primarily because of death and progressive disease. By contrast with our results, minimal to no median overall survival benefit has been observed in trials of sunitinib versus placebo (17·0 *vs* 14·9 months, respectively; p=0·161) or regorafenib versus placebo (17·4 *vs* 17·4 months, respectively; p=0·572) as second-line or third-line therapies in the respective pivotal trials in which crossover also occurred.[4,5] The rapid clinical decline in patients who received placebo, which might have prevented approximately a third of patients from crossing over to the ripretinib group, highlights the need for new treatments and might ultimately limit the use of placebo controls in future studies evaluating treatments that are equal or superior to fourth-line therapies in gastrointestinal stromal tumour.

In our study, a specific mutational status was not required for patient enrolment. The frequency of primary mutations and *KIT* and *PDGFRA* wild-type, excluding the 17 patients for whom mutational status was not available or not done, was consistent with those reported in the literature with the exception of a slight increase in primary exon 9 mutations and a lower frequency of *PDGFRA* mutations.[18,28] Although the prevalence of secondary mutations is not reported in this Article, secondary resistance mutations in patients who have gastrointestinal stromal tumours usually occur in the kinase switch pocket (encoded by *KIT* exons 13 and 14 or *PDGRA* exons 14 and 15) or in the activation loop switch (encoded by *KIT* exons 17 and 18 and *PDGFRA* exon 18) and lead to dysregulated switch function and loss of physiological

conformational control.[10,20,29,30] By contrast with sunitinib and regorafenib, which are selectively active for secondary *KIT* exon 13 and 14 mutations or a subset of secondary *KIT* exon 17 mutations, respectively, ripretinib showed broad preclinical activity.[8,12,15,31] In this study, which included an unselected population of patients with advanced gastrointestinal stromal tumours, including ten (8%) of 129 patients with *KIT* and *PDGFRA* wild-type mutational status, ripretinib significantly improved median progression-free survival and had activity in fourth-line (or further line) treatment of gastrointestinal stromal tumours, in which a variety of secondary mutations might be expected to have been observed.

The safety profile of ripretinib was acceptable. One of the most common treatment-related treatment-emergent adverse events reported with ripretinib was alopecia, which was primarily grade 1 and grade 2. One patient had treatment interruption because of alopecia. Compared with the overall treatment-related alopecia incidence in 42 (49%) of 85 patients, alopecia with ripretinib was reported more in female patients, perhaps due to reporting bias, although this was not formally assessed. Although alopecia in patients with advanced gastrointestinal stromal tumours has also been reported with imatinib and regorafenib, the incidence in our study was higher than those agents.[15,32] The pathogenesis of alopecia with ripretinib is unclear, but might be due to differences in the target kinases inhibited, the effect on associated downstream pathways, and the role that targeted molecules might play in hair follicle biology.[33–36] In in-vitro studies, ripretinib inhibited kinases (eg, KIT, PDGFRA, VEGFR2, and BRAF) that have been associated with alopecia.[20,34,36] Similarly, treatment-related palmar–plantar erythrodysesthesia was reported in 18 (21%) of 85 patients who received ripretinib, but events were limited to grade 1 and grade 2. Palmar–plantar erythrodysesthesia in patients with advanced gastrointestinal stromal tumours has also been reported with sunitinib (19 [9%] of 202 patients at grade 1 or 2, and nine [4%] of 202 patients at grade 3) and regorafenib (74 [56%] of 132 patients at any grade, and 26 [20%] of 132 patients at grade 3).[14,15] Palmar–plantar erythrodysesthesia was managed with routine care of the affected skin area, with one patient discontinuing study treatment because of treatment-related palmar–plantar erythrodysesthesia.

Limitations of our study included the small sample size, which made stratifying patients by more baseline parameters difficult. Our study also allowed crossover from the group receiving placebo to the group receiving ripretinib at progressive disease, which prevented a pure placebo group in the overall survival assessment. Although the nominal p values of overall survival and QOL endpoints are less than 0·05 and the treatment difference is clinically meaningful, statistical significance cannot be claimed for these endpoints because of the prespecified hierarchal statistical testing procedure. However, the design of our study afforded particular strengths, such as the placebo-controlled approach.

In conclusion, results from the INVICTUS study showed the efficacy and safety of ripretinib as fourth-line (or further-line) therapy in patients who have advanced gastrointestinal stromal tumours. In May, 2020, the US FDA approved ripretinib for the treatment of adult patients with advanced gastrointestinal stromal tumours who have received previous treatment with three or more kinase inhibitors, including imatinib.[37] Ripretinib is being evaluated in an ongoing phase 3 study (INTRIGUE) in second-line treatment compared with sunitinib (NCT03673501).

Contributors

J-YB, CS, MCH, JZ, SB, HG, PS, RLJ, SA, GD, PC, PR, SG, and MvM were involved in the collection of data and contributed to the provision of study materials and patients. KS did the statistical analysis. J-YB and MvM participated in the writing of the study protocol. All authors contributed to the interpretation of data, critical review, editing, revision of manuscript drafts, and approval of the final version.

Declaration of interests

J-YB reports grants and personal fees from Deciphera Pharmaceuticals during the study; grants and personal fees from Novartis, Pfizer, and Bayer; and grants from Blueprint Medicines, outside the submitted work. CS reports grants (laboratory research) and personal fees (advisory board) from Deciphera Pharmaceuticals during the study; grants (laboratory research grant), personal fees (lectures), and financial support (travel grant) from Bayer AG; grants (laboratory research grant) and financial support (travel grant) from Pfizer; personal fees (lecture; advisory role) from Blueprint medicines; and financial support (travel grants) from Pharmamar, Novartis, and Lilly, outside the submitted work. MCH reports grants and personal fees from Deciphera Pharmaceuticals during the study; personal fees (consulting) and equity interest from MolecularMD; personal fees from Novartis (consulting, expert testimony); and grants and personal fees (consulting) from Blueprint Medicines, outside the submitted work. MCH also has a patent "Treatment of gastrointestinal stromal tumors" licensed to Novartis. JZ reports stock from GW Pharmaceuticals, Aimmune, Vertex, Bluebird Bio, Alnylam, Biomarin, Sage Therapeutics, Dova Pharmaceuticals, Therapeutics MD, Juno Therapeutics, Kite Pharma, Kiadis Pharma, CSL Limited, Cochlear, QURE, Sangamo Therapeutics, and Frequency Therapeutics; grants (to institution) and honoraria, consulting and advisory role from Pfizer; grants (to institution) and honoraria, consulting and advisory role, and travel and accommodation support from Merck Serono; grants (to institution) and honoraria from Specialized Therapeutics; honoraria and a consulting and advisory role from Targovax and Halozyme; honoraria from Gilead Sciences and Quantium HealthCare; grants (to institution) and consulting and advisory role, and travel and accommodation support from Merck; consulting and advisory role for Sirtex Medical, Lipotek, and 1GlobalHealth; grants (to institution) from Bayer, Roche, Bristol-Myers Squibb, Baxalta and Shire, and Lilly; grants (to institution) and travel and accommodation support from AstraZeneca; and travel and accommodation support from Deciphera Pharmaceuticals, outside the submitted work. SB reports personal fees (advisory board) from Deciphera Pharmaceuticals; grants (research support) from Incyte; grants (research support) and personal fees (advisory board) from Blueprint Medicines; personal fees (Continuing Medical Education-honoraria, travel support) from Pharmamar, personal fees (advisory board) from ADC Therapeutics, Nanobiotix, Bayer, Exelixis, Daiichi-Sankyo, and Roche, personal fees (advisory board, Continuing Medical Education-honoraria) from Lilly, grants (research support) and personal fees (Continuing Medical Education, advisory board) from Novartis, outside the submitted work. HG reports participation in sponsored studies and fees for an advisory role paid to institution from Deciphera Pharmaceuticals, during the study. PS reports personal fees from Deciphera Pharmaceuticals, during the study; and institutional

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Data sharing

Deciphera will share the redacted INVICTUS study protocol online. Qualified scientific and medical researchers can make requests for individual participant data that underlie the results reported in this Article, after de-identification, at info@deciphera.com. Proposals for data will be evaluated and approved by Deciphera in its sole discretion. All approved researchers must sign a data access agreement before 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 after article publication. Deciphera will not share data from identified participants or a data dictionary.

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