Ripretinib versus sunitinib in patients with advanced gastrointestinal stromal tumor after treatment with imatinib (INTRIGUE) a randomized, open-label, phase III trial

Bauer, S.; Jones, R.L.; Blay, J.Y.; Gelderblom, H.; George, S.; Schoffski, P.; ... ; Heinrich, M.C.

original reports

Ripretinib Versus Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumor After Treatment With Imatinib (INTRIGUE): A Randomized, Open-Label, Phase III Trial

Sebastian Bauer, MD[1,2]; Robin L. Jones, MD, MBBS[3]; Jean-Yves Blay, MD, PhD[4]; Hans Gelderblom, MD, PhD[5]; Suzanne George, MD[6]; Patrick Schöffski, MD[7]; Margaret von Mehren, MD[8]; John R. Zalcberg, MD, PhD[9]; Yoon-Koo Kang, MD, PhD[10]; Albiruni Abdul Razak, MRCP, MBBCh[11]; Jonathan Trent, MD, PhD[12]; Steven Attia, DO[13]; Axel Le Cesne, MD[14]; Ying Su, MD, PhD[15]; Julie Meade, MD[15]; Tao Wang, PhD[15]; Matthew L. Sherman, MD[15]; Rodrigo Ruiz-Soto, MD[15]; and Michael C. Heinrich, MD[16,17]

abstract

PURPOSE Sunitinib, a multitargeted tyrosine kinase inhibitor (TKI), is approved for advanced gastrointestinal stromal tumor (GIST) after imatinib failure. Ripretinib is a switch-control TKI approved for advanced GIST after prior treatment with three or more TKIs, including imatinib. We compared efficacy and safety of ripretinib versus sunitinib in patients with advanced GIST who were previously treated with imatinib (INTRIGUE, ClinicalTrials.gov identifier: NCT03673501).

PATIENTS AND METHODS Random assignment was 1:1 to once-daily ripretinib 150 mg or once-daily sunitinib 50 mg (4 weeks on/2 weeks off) and stratified by *KIT*/*platelet-derived growth factor* α mutation and imatinib intolerance. The primary end point was progression-free survival (PFS) by independent radiologic review using modified Response Evaluation Criteria in Solid Tumors version 1.1. Secondary end points included objective response rate by independent radiologic review, safety, and patient-reported outcome measures.

RESULTS Overall, 453 patients were randomly assigned to ripretinib (intention-to-treat [ITT], n = 226; *KIT* exon 11 ITT, n = 163) or sunitinib (ITT, n = 227; *KIT* exon 11 ITT, n = 164). Median PFS for ripretinib and sunitinib (*KIT* exon 11 ITT) was 8.3 and 7.0 months, respectively (hazard ratio, 0.88; 95% CI, 0.66 to 1.16; $P = .36$); median PFS (ITT) was 8.0 and 8.3 months, respectively (hazard ratio, 1.05; 95% CI, 0.82 to 1.33; nominal $P = .72$). Neither was statistically significant. Objective response rate was higher for ripretinib versus sunitinib in the *KIT* exon 11 ITT population (23.9% *v* 14.6%, nominal $P = .03$). Ripretinib was associated with a more favorable safety profile, fewer grade 3/4 treatment-emergent adverse events (41.3% *v* 65.6%, nominal $P < .0001$), and better scores on patient-reported outcome measures of tolerability.

CONCLUSION Ripretinib was not superior to sunitinib in terms of PFS. However, meaningful clinical activity, fewer grade 3/4 treatment-emergent adverse events, and improved tolerability were observed with ripretinib.

J Clin Oncol 40:3918-3928. © 2022 by American Society of Clinical Oncology

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Protocol

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

Accepted on June 20, 2022 and published at ascopubs.org/journal/jco on August 10, 2022: DOI https://doi.org/10.1200/JCO.22.00294

INTRODUCTION

Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the gastrointestinal tract (10-15 cases/million annually) with 80%-90% being driven by activating genomic alterations in *KIT* or platelet-derived growth factor α (*PDGFRA*).[1-6] First-line treatment with imatinib—a KIT and PDGFRA tyrosine kinase inhibitor (TKI)—results in initial tumor response and disease control; however, nearly all patients eventually progress.[7-10]

Sunitinib is a multitargeted TKI with activity against the vascular endothelial growth factor receptor.[11] It was approved in 2006 for second-line treatment of patients with GIST following progression on or intolerance to imatinib.[12] Sunitinib is active against secondary mutations in *KIT* exons 13/14 (ATP-binding pocket), but less active against exons 17/18 (activation loop), yielding an overall median progression-free survival (PFS) of 5.6 months for molecularly unselected patients with advanced GIST in the historical registration trial.[12-14] Given the heterogeneous nature of *KIT* and *PDGFRA* resistance mutations in GIST, there is an unmet need for an effective broad-spectrum TKI in early treatment.[15]

Ripretinib is a switch-control TKI with a dual mechanism of action that provides broad-spectrum inhibition of KIT or PDGFRA activity.[16] It is approved for the treatment of patients with advanced GIST who

CONTEXT

Key Objective

The phase III INTRIGUE study evaluated efficacy and safety of ripretinib compared with sunitinib as a second-line therapy for patients with advanced gastrointestinal stromal tumor who were previously treated with imatinib. INTRIGUE is the largest randomized phase III trial in the second-line setting in advanced gastrointestinal stromal tumor with an active comparator arm.

Knowledge Generated

Although ripretinib was not superior to sunitinib in terms of progression-free survival (primary end point), meaningful clinical activity was observed. Patients receiving ripretinib experienced fewer grade 3/4 treatment-emergent adverse events compared with patients receiving sunitinib. Ripretinib was also associated with better scores on patient-reported outcome measures of tolerability.

Relevance

There was no significant difference in median progression-free survival between ripretinib and sunitinib. Ripretinib had a more favorable safety profile and a higher response rate compared with sunitinib. Longer follow-up is needed to assess overall survival.

received prior treatment with three or more TKIs, including imatinib, on the basis of the results of the phase III INVICTUS study.[17,18] Phase I data suggest ripretinib is effective as second-line therapy in patients with advanced GIST (median PFS: 10.7 months).[19] Ripretinib had higher activity against imatinib-resistant secondary *KIT* mutations in vitro versus sunitinib, suggesting that ripretinib may be superior in second-line GIST.[16] In this phase III INTRIGUE study, we evaluate the efficacy and safety of ripretinib versus sunitinib in patients with advanced GIST previously treated with imatinib.

PATIENTS AND METHODS

Study Design

INTRIGUE (ClinicalTrials.gov identifier: NCT03673501) is a randomized, open-label, international, multicenter phase III study comparing efficacy and safety of ripretinib versus sunitinib in patients with advanced GIST who progressed on or were intolerant to first-line treatment with imatinib. This study used a biomarker-positive/overall group design in which end points were assessed in two populations.[20,21] INTRIGUE was active at 122 sites in 22 countries. Patients were stratified by mutational status (*KIT* exon 11, *KIT* exon 9, *KIT*/*PDGFRA* wild-type [WT], and other *KIT* [other than exon 9 or exon 11]/*PDGFRA* mutations) and imatinib intolerance and subsequently randomly assigned (1:1) to receive once-daily ripretinib 150 mg (continuous dosing) or once-daily sunitinib 50 mg, 4 weeks on/2 weeks off (4/2) in 6-week cycles. Crossover was not allowed.

Patients requiring dose interruptions $>$ 28 consecutive days were discontinued from treatment. With ripretinib, first and second dose reductions were once-daily 100 mg and once-daily 50 mg, respectively. Dose modifications for sunitinib were per approved prescribing information or institutional guidelines (Data Supplement, online only).

This study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Guidelines for Good Clinical Practice. The Protocol (online only), protocol amendments, and informed consent documents were approved by an institutional review board or ethics committee at each site and by appropriate regulatory authorities. Patients provided written informed consent.

Eligibility Criteria

Eligible patients were age $\geq$ 18 years, had histologically confirmed GIST with $\geq$ 1 measurable lesion by modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST v1.1; modifications followed those described by Demetri et al[22]) within 21 days before administration of study drug, provided an archival tissue sample and pathology report containing *KIT/PDGFRA* mutation status using a tissue-based PCR or other DNA sequencing assay, had disease progression on or documented intolerance to imatinib, had imatinib treatment discontinued 10 days before first dose of study drug, and had an Eastern Cooperative Oncology Group performance status (ECOG PS) $\leq$ 2 with adequate organ function and bone marrow reserve. Complete inclusion/exclusion criteria are provided in the Data Supplement.

Outcomes

The primary end point was PFS by independent radiologic review (IRR) using mRECIST v1.1 and was tested in the two intention-to-treat (ITT) populations of *KIT* exon 11 participants and all patients. PFS was defined as time between random assignment and first disease progression or death because of any cause, whichever occurred first. PFS was censored on the date of the last adequate disease assessment for patients with no event. Key secondary end

points were objective response rate (ORR) by IRR using mRECIST v1.1 and overall survival (OS), and were also analyzed for both the *KIT* exon 11 ITT and overall ITT populations. Other secondary end points included safety, PFS by investigator, and quality of life (QoL). The ITT population, defined as all randomly assigned patients who provided informed consent, was used for efficacy analyses. The safety population was defined as all patients who received ≥ 1 dose of study drug. End point definitions are available in the Data Supplement.

Assessments

Tumor assessments (CT or MRI) were completed at screening, Day (D) 1 of Cycles (C) 2-7, every other cycle thereafter, and end-of-treatment visit. Following C7 D1, an initial indication of a partial response or CR on the basis of investigator assessment must also be confirmed ≥ 4 weeks following the initial response. After treatment discontinuation, patients and families were contacted by phone every 3 months for survival data.

The safety profile was based on physical examinations, clinical laboratory tests, ECOG PS, changes from baseline in vital signs, electrocardiograms, left ventricular ejection fraction, dermatologic examinations, and adverse event (AE) reporting. Safety evaluations included treatment-emergent AEs (TEAEs), serious AEs (SAEs), treatment-related TEAEs, dose interruptions, dose reductions, and study drug discontinuations. AE severity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. AEs were monitored from informed consent to safety follow-up (30 days after last dose); AEs were considered treatment emergent if they occurred after administration of first dose of study drug and through 30 days after last dose of study drug or the day before start of subsequent new anticancer drug, whichever occurred first. Drug-related AEs reported after 30 days after the last dose of study drug were also considered TEAEs.

QoL was assessed with patient-reported outcome (PRO) measures (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer-30 and Dermatology Life Quality Index).[23,24]

Statistical Analyses

Approximately 426 patients and 262 PFS events in the ITT population were calculated to provide 90% power to detect a

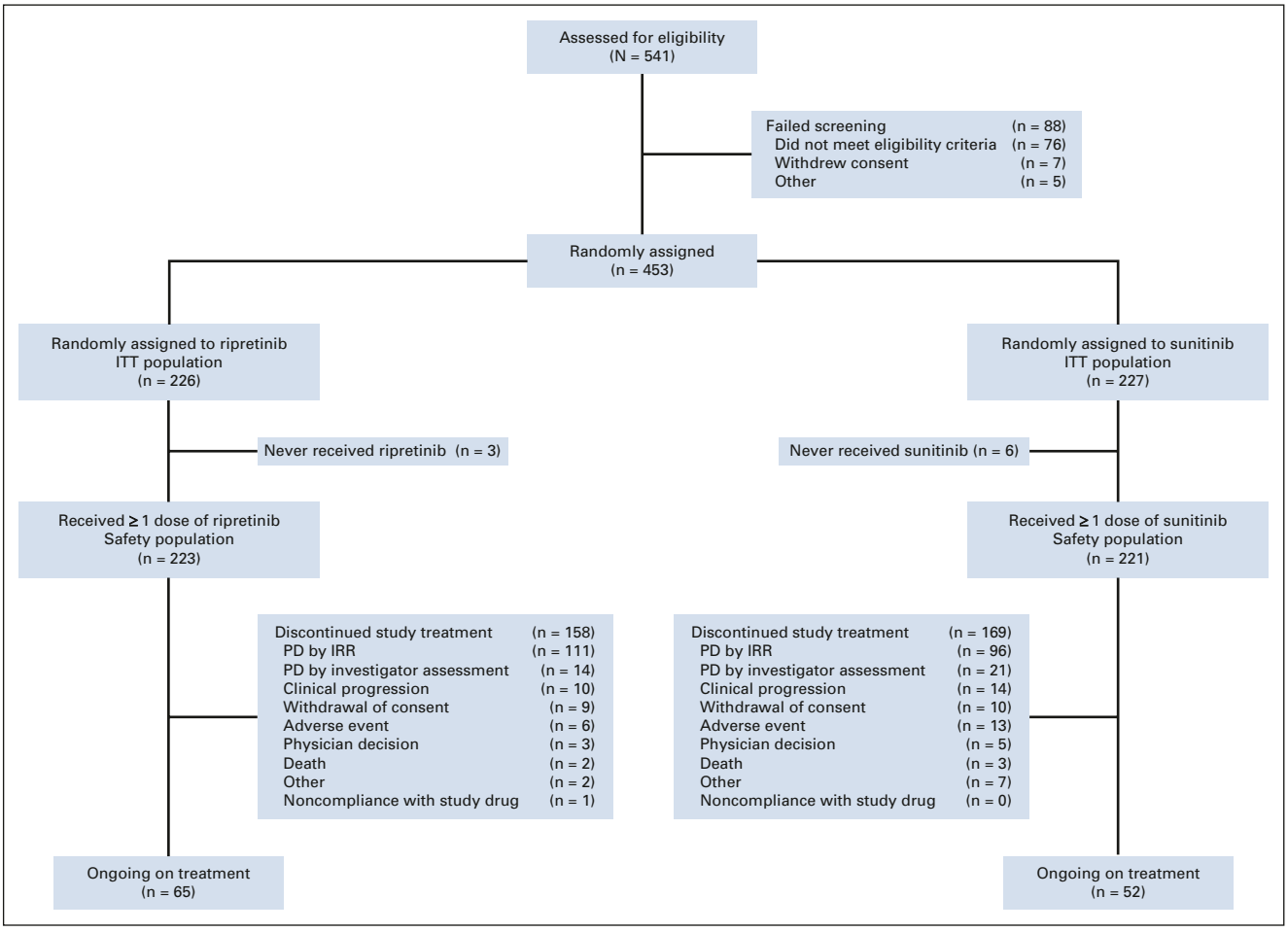


FIG 1. CONSORT diagram for the phase III INTRIGUE study. IRR, independent radiologic review; ITT, intention-to-treat; PD, progressive disease.

50% improvement in PFS (median PFS ripretinib: 9 months; sunitinib: 6 months; hazard ratio [HR], 0.667) with a two-sided alpha of .05. In the *KIT* exon 11 ITT population, 151 PFS events were estimated to provide 95% power to detect an 80% PFS improvement (median PFS ripretinib: 9 months; sunitinib: 5 months; HR, 0.556) with a two-sided alpha of .05.

To control familywise type I error at a two-sided 0.05 level, hypothesis testing followed a hierarchical sequence: primary end point PFS, then key secondary end points ORR followed by OS. Within each end point, the *KIT* exon 11 ITT population was tested before the overall ITT population. If a testing in the sequence failed to meet statistical significance, subsequent *P* values were considered nominal.[25] Therefore, outcomes for the *KIT* exon 11 ITT population are presented first followed by the overall ITT population.

Time-to-event data were summarized using the Kaplan-Meier method with associated two-sided 95% CIs. HRs and *P* values were obtained from stratified Cox regression model and two-sided stratified log-rank tests, respectively. The associated 95% CI for PFS was obtained using the Wald method. ORR was analyzed by Cochran-Mantel-Haenszel chi-square test for the association between treatment and ORR with 95% CI of the ORR difference calculated using Newcombe method. Descriptive statistics were used to summarize safety data; *P* values reported for safety were not prespecified. An independent data monitoring committee reviewed safety and efficacy data periodically throughout the study. Statistical analyses were done with SAS (version 9.4; Cary, NC) and did not deviate from the statistical analysis plan.

RESULTS

Patients

Overall, 453 patients were randomly assigned to once-daily ripretinib 150 mg (n = 226) or once-daily sunitinib 50 mg (4/2, n = 227; Fig 1). Median age was 60 (range, 18-88) years, 62.0% were male, 66.2% were White, and 46.8% were from Europe (ITT; Table 1). Most patients had a baseline ECOG PS score ≤ 1 (99.1%). A total of 327 patients (72.2%) had a primary *KIT* exon 11 mutation (ripretinib, n = 163; sunitinib, n = 164; *KIT* exon 11 ITT), 60 (13.2%) had a primary *KIT* exon 9 mutation, 33 (7.3%) were *KIT*/*PDGFRA* WT, and 33 (7.3%) had a primary mutation in another *KIT* exon (other than 9 or 11) or a *PDGFRA* mutation. Overall, 9.9% had reported imatinib intolerance. Demographic and clinical characteristics were well balanced between treatment arms (Table 1).

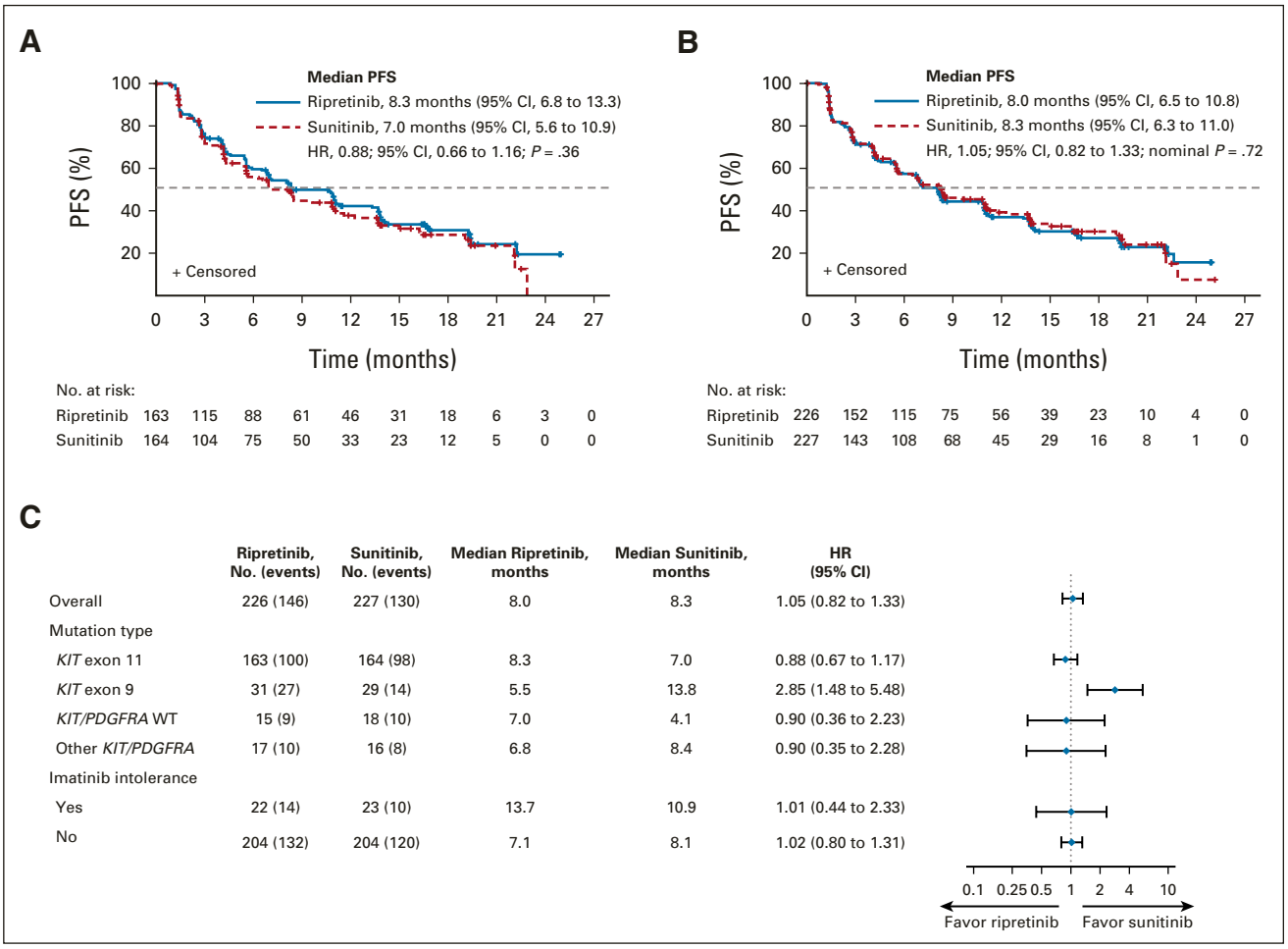
TABLE 1. Patient Demographics and Baseline Characteristics in the ITT Population

Characteristic	Ripretinib (n = 226)	Sunitinib (n = 227)	Total (N = 453)
Age, years, median (min, max)	59.5 (18, 86)	60 (26, 88)	60 (18, 88)
Sex, male, No. (%)	139 (61.5)	142 (62.6)	281 (62.0)
Race, White, No. (%)	148 (65.5)	152 (67.0)	300 (66.2)
Region, No. (%)			
North America	87 (38.5)	76 (33.5)	163 (36.0)
South America	7 (3.1)	11 (4.8)	18 (4.0)
Europe	102 (45.1)	110 (48.5)	212 (46.8)
Asia-Pacific	30 (13.3)	30 (13.2)	60 (13.2)
ECOG PS, No. (%)			
0	131 (58.0)	128 (56.4)	259 (57.2)
1	92 (40.7)	98 (43.2)	190 (41.9)
2	3 (1.3)	1 (0.4)	4 (0.9)
Mutation,[a] No. (%)			
KIT exon 11	163 (72.1)	164 (72.2)	327 (72.2)
KIT exon 9	31 (13.7)	29 (12.8)	60 (13.2)
KIT/*PDGFRA* WT	15 (6.6)	18 (7.9)	33 (7.3)
Other *KIT*/*PDGFRA*[b]	17 (7.5)	16 (7.0)	33 (7.3)
Imatinib intolerance,[a] No. (%)	22 (9.7)	23 (10.1)	45 (9.9)
Sum of longest diameters of target lesions, mm, median (min, max)	93.1 (11, 459)	84.1 (15, 418)	90.5 (11, 459)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; max, maximum; min, minimum; *PDGFRA*, platelet-derived growth factor α; WT, wild-type.

[a]On the basis of interactive response technology stratification.

[b]Other *KIT* included any patient with a *KIT* mutation other than exon 9 or exon 11.



	Ripretinib, No. (events)	Sunitinib, No. (events)	Median Ripretinib, months	Median Sunitinib, months	HR (95% CI)
Overall	226 (146)	227 (130)	8.0	8.3	1.05 (0.82 to 1.33)
Mutation type					
KIT exon 11	163 (100)	164 (98)	8.3	7.0	0.88 (0.67 to 1.17)
KIT exon 9	31 (27)	29 (14)	5.5	13.8	2.85 (1.48 to 5.48)
KIT/PDGFRA WT	15 (9)	18 (10)	7.0	4.1	0.90 (0.36 to 2.23)
Other *KIT/PDGFRA*	17 (10)	16 (8)	6.8	8.4	0.90 (0.35 to 2.28)
Imatinib intolerance					
Yes	22 (14)	23 (10)	13.7	10.9	1.01 (0.44 to 2.33)
No	204 (132)	204 (120)	7.1	8.1	1.02 (0.80 to 1.31)

FIG 2. Kaplan-Meier analysis of PFS for patients treated with ripretinib or sunitinib in the (A) *KIT* exon 11 ITT population and (B) the ITT population; (C) forest plot of PFS by stratification factors for patients treated with ripretinib or sunitinib. HRs were obtained from stratified Cox regression model and *P* values were from two-sided stratified log-rank tests. HR, hazard ratio; ITT, intention-to-treat; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; WT, wild-type.

Efficacy

Ripretinib did not demonstrate statistically significant improvement over sunitinib in PFS by IRR in the *KIT* exon 11 ITT (HR, 0.88; 95% CI, 0.66 to 1.16; $P = .36$; median 8.3 *v* 7.0 months; Fig 2A) or ITT population (HR, 1.05; 95% CI, 0.82 to 1.33; nominal $P = .72$; median 8.0 *v* 8.3 months; Fig 2B) at the data cutoff (September 1, 2021). Similar results were observed in sensitivity analyses. In the *KIT* exon 11

TABLE 2. ORR and DOR in Patients Treated With Ripretinib Versus Sunitinib

	KIT Exon 11 ITT Population		ITT Population	
Parameter	**Ripretinib (n = 163)**	**Sunitinib (n = 164)**	**Ripretinib (n = 226)**	**Sunitinib (n = 227)**
ORR, No. (%) 95% CI	39 (23.9) 17.6 to 31.2	24 (14.6) 9.6 to 21.0	49 (21.7) 16.5 to 27.6	40 (17.6) 12.9 to 23.2
CR, No. (%)[a]	0	2 (1.2)	1 (0.4)	3 (1.3)
PR, No. (%)[b]	39 (23.9)	22 (13.4)	48 (21.2)	37 (16.3)
Difference in ORR, % (95% CI)	9.3 (0.7 to 17.8)		4.2 (−3.2 to 11.5)	
P[c]	.03		.27	
DOR, months, median (95% CI)	16.7 (12.5 to NE)	20.1 (11.0 to NE)	16.7 (12.5 to NE)	20.1 (12.3 to NE)

Abbreviations: CR, complete response; DOR, duration of response; ITT, intention-to-treat; mRECIST, modified RECIST; NE, not estimable; ORR, objective response rate; PR, partial response.

[a]Disappearance of all target lesions; any pathologic lymph nodes (nontarget per mRECIST) must have reduction in short axis to < 10 mm.

[b]At least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

[c]ORR was analyzed using the Cochran-Mantel-Haenszel chi-square test; *P* values reported are nominal and no statistical significance can be claimed.

TABLE 3. Exposure and AE Overview in the Safety Population

Parameter	Ripretinib (n = 223)	Sunitinib (n = 221)
Treatment duration, months		
Mean (SD)	9.1 (6.65)	8.1 (6.28)
Median (range)	7.9 (0.20-26.45)	6.5 (0.20-26.32)
Any dose modification, No. (%)	85 (38.1)	140 (63.3)
Any dose reduction	44 (19.7)	111 (50.2)
Any dose interruption	62 (27.8)	84 (38.0)
Sunitinib dose regimen modification,[a] No. (%)		
No	NA	174 (78.7)
Yes	NA	47 (21.3)
Continuous dosing	NA	33 (14.9)
Other	NA	19 (8.6)
Any TEAE,[b] No. (%)	221 (99.1)	219 (99.1)
Any grade 3/4 TEAE	92 (41.3)	145 (65.6)
Any drug-related TEAE, No. (%)	211 (94.6)	214 (96.8)
Any grade 3/4 drug-related TEAE	59 (26.5)	122 (55.2)
Any treatment-emergent SAE, No. (%)	57 (25.6)	57 (25.8)
Any drug-related treatment-emergent SAE	17 (7.6)	20 (9.0)
Any TEAE leading to dose reduction, No. (%)	45 (20.2)	106 (48.0)
Any TEAE leading to dose interruption, No. (%)	65 (29.1)	92 (41.6)
Any TEAE leading to study treatment discontinuation, No. (%)	8 (3.6)	17 (7.7)
Any TEAE leading to death, No. (%)	4 (1.8)	5 (2.3)
Any drug-related TEAE leading to death	0	1 (0.5)

Abbreviations: AE, adverse event; NA, not applicable; SAE, serious AE; SD, standard deviation; TEAE, treatment-emergent AE.

[a]Modification from the standard 4 weeks on/2 weeks off schedule.

[b]AEs were labeled and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; AEs were considered treatment emergent if they occurred after administration of the first dose of study drug through 30 days after the last dose of study drug.

population, median PFS by investigator was 13.3 months for ripretinib and 10.8 months for sunitinib (HR, 0.92; 95% CI, 0.68 to 1.24; nominal $P = .57$); median PFS by investigator in the ITT population for ripretinib and sunitinib was 10.6 and 10.3 months, respectively (HR, 1.03; 95% CI, 0.80 to 1.34; nominal $P = .81$).

ORR in the *KIT* exon 11 ITT population was 23.9% with ripretinib and 14.6% with sunitinib (nominal $P = .03$; Table 2); ORR in the ITT population was 21.7% with ripretinib versus 17.6% with sunitinib (nominal $P = .27$; Table 2). Median duration of response for ripretinib and sunitinib in both populations was 16.7 and 20.1 months, respectively (Table 2).

OS data were highly immature with event rates of 21.1% and 22.3% in the *KIT* exon 11 ITT and overall ITT populations, respectively. The median OS was not reached for either arm. Mature OS data will be presented in a subsequent publication.

PFS subgroup analyses on the basis of stratification factors revealed that patients with primary *KIT* exon 9 mutations (n = 60) were the only subgroup in which PFS benefit favored treatment with sunitinib versus ripretinib (HR, 2.85; 95% CI, 1.48 to 5.48; median 13.8 *v* 5.5 months; Fig 2C, Data Supplement).

Safety

Ripretinib was generally well tolerated and its safety profile was consistent with existing prescribing information (Table 3).[18] In the safety population (ripretinib, n = 223; sunitinib, n = 221), the most common TEAEs with ripretinib were alopecia (64.1%), fatigue (37.7%), and myalgia (36.3%). Palmar-plantar erythrodysesthesia syndrome (PPES; 51.1%), diarrhea (48.0%), and hypertension (47.1%) were the most common with sunitinib (Table 4).

Fewer patients had grade 3/4 TEAEs with ripretinib (n = 92, 41.3%) compared with sunitinib (n = 145, 65.6%; nominal $P < .0001$; Table 3, Fig 3). Similarly, there were fewer patients with grade 3/4 drug-related TEAEs with ripretinib (n = 59, 26.5%) compared with sunitinib (n = 122, 55.2%; Table 3). Grade 3/4 TEAEs (≥ 2% of patients in either arm) were mostly lower with ripretinib versus sunitinib and included hypertension (8.5% *v* 26.7%), neutropenia or neutrophil count decreased (0% *v* 13.1%), PPES (1.3% *v* 10%), diarrhea (0.9% *v* 2.7%), hypertriglyceridemia (0.4% *v* 3.2%), lymphocyte count decreased (0.4% *v* 2.3%), and stomatitis (0% *v* 2.7%; Fig 3). Hypertension was the single most common grade 3/4 drug-related TEAE in either arm; however, patients receiving sunitinib were nearly four times more likely to develop drug-related grade 3/4 hypertension (22.6%) compared with ripretinib (5.8%). There were no drug-related TEAEs leading to death with ripretinib and one with sunitinib (intracranial hemorrhage; Table 3).

Fewer patients who received ripretinib needed dose modifications (38.1%) versus sunitinib (63.3%; Table 3). Dose interruptions, dose reductions, and treatment discontinuations because of TEAEs were lower with ripretinib (29.1%, 20.2%, and 3.6%) versus sunitinib (41.6%, 48.0%, and 7.7%; Table 3). The incidence of treatment-emergent SAEs was similar between ripretinib (25.6%) and sunitinib (25.8%). Overall, 7.6% and 9.0% of patients experienced drug-related treatment-emergent SAEs with ripretinib and sunitinib, respectively (Table 3).

Quality of Life

Because of high incidence of dermatologic AEs reported with sunitinib, patients used the Dermatology Life Quality Index to

TABLE 4. TEAEs[a] of ≥ 20% in Either Treatment Arm

	Ripretinib (n = 223)		Sunitinib (n = 221)	
Preferred Term	**All Grades, No. (%)**	**Grade 3/4, No. (%)**	**All Grades, No. (%)**	**Grade 3/4, No. (%)**
Alopecia	143 (64.1)	NA[b]	18 (8.1)	NA[b]
Fatigue	84 (37.7)	7 (3.1)	91 (41.2)	4 (1.8)
Myalgia	81 (36.3)	4 (1.8)	24 (10.9)	0
Constipation	78 (35.0)	1 (0.4)	48 (21.7)	0
Decreased appetite	60 (26.9)	2 (0.9)	54 (24.4)	2 (0.9)
Hypertension	59 (26.5)	19 (8.5)	104 (47.1)	59 (26.7)
Palmar-plantar erythrodysesthesia	59 (26.5)	3 (1.3)	113 (51.1)	22 (10.0)
Abdominal pain	58 (26.0)	6 (2.7)	38 (17.2)	6 (2.7)
Muscle spasms	55 (24.7)	1 (0.4)	12 (5.4)	0
Nausea	53 (23.8)	2 (0.9)	56 (25.3)	1 (0.5)
Pruritus	48 (21.5)	1 (0.4)	16 (7.2)	0
Diarrhea	42 (18.8)	2 (0.9)	106 (48.0)	6 (2.7)
Stomatitis	15 (6.7)	0	80 (36.2)	6 (2.7)

Abbreviations: AE, adverse event; NA, not applicable; TEAE, treatment-emergent AE.

[a]AEs were labeled and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; AEs were considered treatment emergent if they occurred after administration of the first dose of study drug through 30 days after the last dose of study drug.

[b]The highest-grade severity for alopecia is grade 2.

assess impact of skin issues on QoL. Impact on QoL was less frequently reported with ripretinib versus sunitinib across treatment cycles (C7 D29: 14.3% *v* 26.0%; Data Supplement). Patients receiving sunitinib also experienced greater deterioration in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer-30 role functioning (ability to work or engage in leisure activities) across all treatment cycles (mean change from baseline at C7 D29: −8.7 *v* −22.7 for ripretinib *v* sunitinib). In both measures, patients receiving sunitinib reported less impact/deterioration on D1 of each cycle immediately following the 2-week off period compared with D29, whereas ripretinib scores did not demonstrate cyclical variation (Data Supplement). Detailed analysis of QoL data will be presented in a separate publication.

DISCUSSION

To our knowledge, INTRIGUE is the largest randomized phase III trial in second-line GIST with an active comparator arm. Ripretinib did not meet the primary end point of superior PFS versus sunitinib. However, PFS observed with ripretinib was comparable to PFS with sunitinib in the *KIT* exon 11 (8.3 *v* 7.0 months) and ITT populations (8.0 *v* 8.3 months), demonstrating clinical activity of ripretinib in second-line GIST. ORR with ripretinib was higher than with sunitinib in the *KIT* exon 11 population. Additionally, the safety profile observed with ripretinib in INTRIGUE was consistent with existing prescribing information.[18] Patients receiving ripretinib experienced fewer grade 3/4 TEAEs and reported better role functioning and less skin toxicity compared with patients receiving sunitinib.

The design assumption that median PFS would be 6 months for sunitinib may have affected the outcome. The PFS for sunitinib observed in this trial was higher (8.3 months, ITT) than the PFS observed in the original phase III sunitinib trial (5.6 months).[13] In that trial, efficacy end points were evaluated using RECIST, not mRECIST v1.1.[13] Although it may be a function of different versions of RECIST, median baseline tumor burden was notably higher in the original sunitinib trial (233 mm [range, 26-722 mm]) than the current study (sunitinib arm, 84.1 mm [range, 15-418 mm]).[13] Similarly, the original study had fewer patients in the sunitinib arm with imatinib intolerance (4.3%) compared with the current study (10.1%), which likely contributed to higher PFS.[13] Furthermore, the baseline sum of longest diameters of target lesions was larger for ripretinib compared with sunitinib in this study. Taken together, these differences may have contributed to the current efficacy outcomes.

In the current study, sunitinib demonstrated greater PFS benefit in patients harboring a *KIT* exon 9 mutation (13.8 months) compared with an exon 11 mutation (7.0 months). This finding is in line with previous studies.[14,26-28] Conversely, patients who received ripretinib in the current study fared better if they had a primary *KIT* exon 11 mutation (8.3 months) versus an exon 9 mutation (5.5 months). In contrast to INVICTUS trial data for ripretinib versus placebo in fourth-line treatment where primary mutation did not predict ripretinib activity, in this study, the primary *KIT* mutation appeared to predict ripretinib activity in second-line treatment.[29] Ripretinib demonstrated good tolerability across all mutation types;

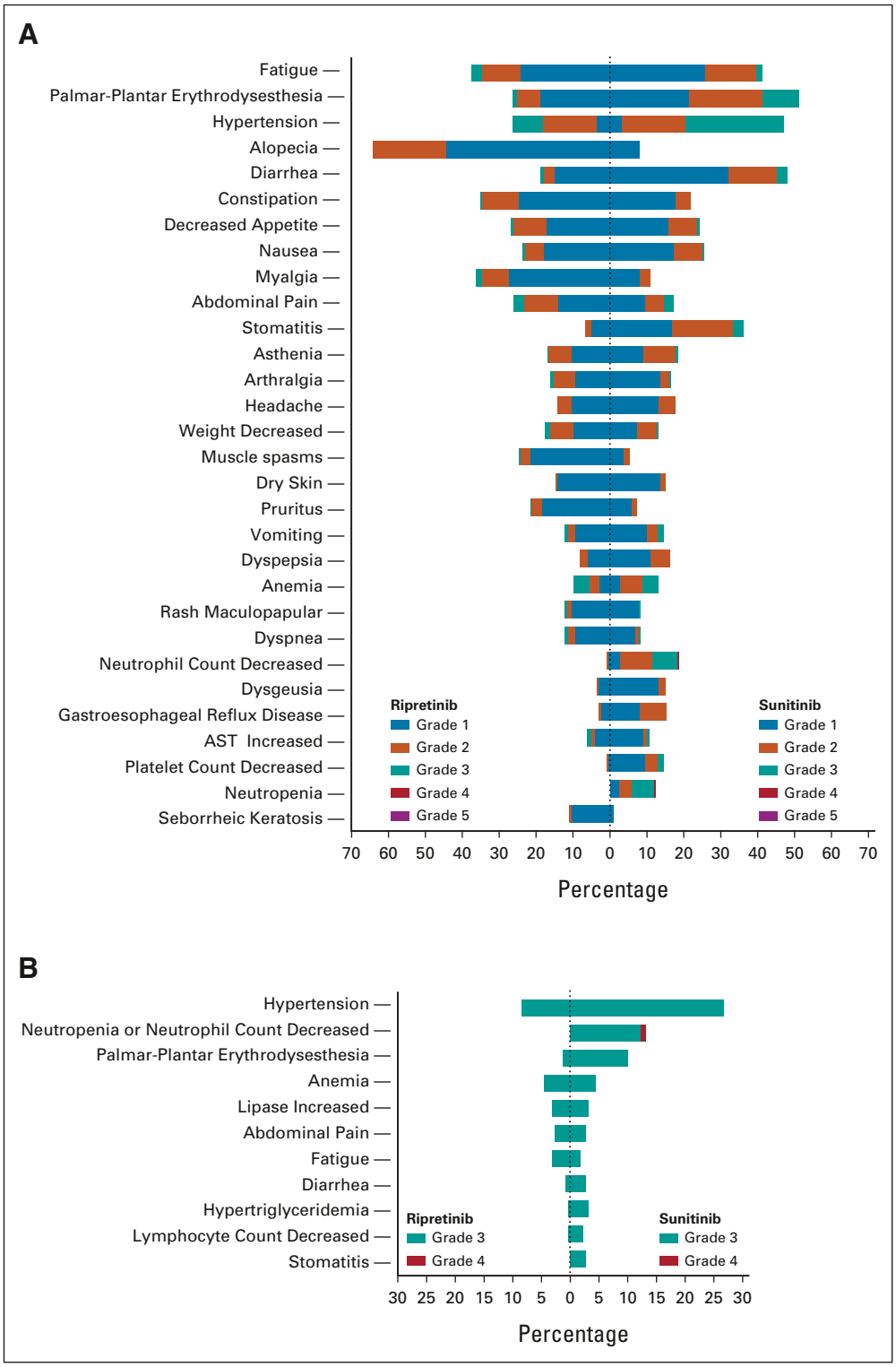


FIG 3. Butterfly plots of TEAEs (≥ 10% in either arm) of (A) all grades and (B) grade 3/4 TEAEs (≥ 2% in either arm). AEs were labeled and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; AEs were considered treatment emergent if they occurred after administration of the first dose of study drug through 30 days after the last dose of study drug. AE, adverse event; TEAE, treatment-emergent AE.

although not tested in this study, similar to imatinib, a higher dose of ripretinib may benefit some patients (particularly those with *KIT* exon 9 mutations) and would be interesting to investigate.[30-32]

Similar to INVICTUS, alopecia was the most common TEAE of any grade observed with ripretinib in INTRIGUE; however, most patients who experienced alopecia were of grade 1 severity (< 50% hair loss).[17,33] Patients who received ripretinib were less likely to experience grade 3/4 TEAEs compared with sunitinib. Additionally, patients receiving sunitinib were more likely to experience TEAEs that are considered clinically impactful and distressing such as stomatitis and diarrhea.[34-36] Even lower-severity diarrhea (moderate or grade 2) can be associated with psychologic distress and limitations in daily living activities, and patients report pain and discomfort with stomatitis/oral mucositis.[33,35,37]

Nearly all grade 3/4 TEAEs (≥ 2% in either arm) were more common with sunitinib (Fig 3B). Patients receiving sunitinib were three times more likely to develop grade 3 hypertension compared with patients receiving ripretinib, increasing the need for closer monitoring to avoid potential exacerbation of prior cardiovascular disease.[33,38] Similarly, patients receiving sunitinib were seven times more likely to develop grade 3 PPES—the highest grade of severity for PPES, characterized by severe skin changes, pain, and limitations in activities of daily living—versus patients receiving ripretinib.[33] PRO measures were also improved with ripretinib versus sunitinib. These results suggest the safety profile of ripretinib is substantially more favorable than that of sunitinib.

Although once-daily 50 mg (4/2) is the recommended starting dose/schedule for sunitinib for patients with GIST, once-daily 37.5-mg continuous dosing is often implemented in clinical practice. This may be due to promising efficacy demonstrated in a small phase II trial (N = 60, median PFS: 34 weeks); however, 23% of patients in this phase II study still required a dose reduction.[39] In a treatment-use study, patients receiving sunitinib who altered their dose or schedule had similar rates of common grade 3/4 TEAEs compared with patients who remained on the once-daily 50-mg (4/2) dose.[40] Without more robust clinical evidence that reduced doses provide at least comparable tolerability and efficacy as the label-recommended dose, patients in INTRIGUE were required to start at once-daily 50 mg (4/2).

Limitations for this study include small sample sizes of additional mutational subgroups (*KIT* exon 9, *KIT*/*PDGFRA* WT, and other *KIT*/*PDGFRA*). The study was powered to investigate the *KIT* exon 11 population, and limited information was available for the other subgroups. Additionally, it is challenging to control familywise type I error for an excessive number of hypothesis tests.

In conclusion, ripretinib was not superior to sunitinib for PFS in patients with advanced GIST previously treated with imatinib. However, median PFS observed with ripretinib was comparable with median PFS observed with sunitinib, suggesting that ripretinib is active as second-line therapy for GIST. Additionally, ORR for patients receiving ripretinib in the *KIT* exon 11 population was higher compared with patients receiving sunitinib. Ripretinib also demonstrated a more favorable safety profile and better responses on PRO measures than sunitinib. Further analysis is ongoing to assess mature OS, pharmacokinetic exposure, circulating tumor DNA, and additional PRO measures.

AFFILIATIONS

[1]Department of Medical Oncology and Sarcoma Center, University Hospital Essen, Essen, Germany
[2]German Cancer Consortium (DKTK), Partner Site Essen, Germany
[3]Sarcoma Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, United Kingdom
[4]Centre Léon Bérard, Lyon, France
[5]Leiden University Medical Center, Leiden, the Netherlands
[6]Dana-Farber Cancer Institute, Boston, MA
[7]Department of General Medical Oncology, Leuven Cancer Institute, KU Leuven, University Hospitals Leuven, Leuven, Belgium
[8]Fox Chase Cancer Center, Philadelphia, PA
[9]Monash University School of Public Health and Preventive Medicine and Department of Medical Oncology, Alfred Health, Melbourne, Victoria, Australia
[10]Asan Medical Center, University of Ulsan, Seoul, South Korea
[11]Toronto Sarcoma Program, Princess Margaret Cancer Center, Toronto, ON, Canada
[12]Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL
[13]Mayo Clinic, Jacksonville, FL
[14]Gustave Roussy, Villejuif, France
[15]Deciphera Pharmaceuticals, LLC, Waltham, MA
[16]Portland VA Health Care System, Portland, OR
[17]OHSU Knight Cancer Institute, Portland, OR

CORRESPONDING AUTHOR

Sebastian Bauer, MD, West German Cancer Center, Internal Medicine Clinic (Tumor Research), Hufelandstraße 55, D–45147 Essen, Germany; Twitter: @seppobauer; e-mail: Sebastian.Bauer@uk-essen.de.

PRIOR PRESENTATION

Presented at the 2022 ASCO Plenary Series, virtual, January 25, 2022.

SUPPORT

The INTRIGUE study was funded by Deciphera Pharmaceuticals, LLC.

CLINICAL TRIAL INFORMATION

NCT03673501 (INTRIGUE)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.00294.

AUTHOR CONTRIBUTIONS

Conception and design: Sebastian Bauer, Robin L. Jones, Jean-Yves Blay, Hans Gelderblom, Suzanne George, Patrick Schöffski, Margaret von Mehren, John R. Zalcberg, Jonathan Trent, Steven Attia, Ying Su, Julie Meade, Tao Wang, Matthew L. Sherman, Rodrigo Ruiz-Soto, Michael C. Heinrich

Provision of study materials or patients: Sebastian Bauer, Robin L. Jones, Jean-Yves Blay, Hans Gelderblom, Suzanne George, Patrick Schöffski, Margaret von Mehren, John R. Zalcberg, Yoon-Koo Kang, Albiruni Abdul Razak, Jonathan Trent, Steven Attia, Axel Le Cesne, Michael C. Heinrich

Collection and assembly of data: All authors

Data analysis and interpretation: All authors

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The INTRIGUE study was funded by Deciphera Pharmaceuticals, LLC. The authors thank the patients and their families and caregivers, the investigators, and the investigational site staff of the INTRIGUE study. Medical writing support was provided by Lauren Hanlon, PhD, of AlphaBioCom, LLC, King of Prussia, PA, and was funded by Deciphera Pharmaceuticals, LLC, in compliance with international good publication practice guidelines. MCH received partial salary support from the following sources: a research grant from the Jonathan David Foundation, a VA Merit Review Grant (I01BX005358), and an NCI R21 grant (R21CA263400). INTRIGUE study investigators are listed in Appendix Table A1 (online only).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Ripretinib Versus Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumor After Treatment With Imatinib (INTRIGUE): A Randomized, Open-Label, Phase III Trial

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Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Sebastian Bauer
Honoraria: Novartis, Pfizer, Bayer, Pharmamar, GlaxoSmithKline, Deciphera
Consulting or Advisory Role: Blueprint Medicines, Bayer, Lilly, Deciphera, Nanobiotix, Daiichi Sankyo, Exelixis, Janssen-Cilag, ADC Therapeutics, Mundipharma, GlaxoSmithKline, Adcendo, Boehringer Ingelheim
Research Funding: Blueprint Medicines, Novartis, Incyte (Inst)
Travel, Accommodations, Expenses: Pharmamar

Yoon-Koo Kang
Consulting or Advisory Role: DAEHWA Pharmaceutical, Bristol Myers Squibb, Zymeworks, ALX Oncology, Amgen, Novartis, Macrogenics, Surface Oncology, Blueprint Medicines

Tao Wang
Employment: Deciphera
Stock and Other Ownership Interests: Deciphera, Pfizer

Robin L. Jones
Consulting or Advisory Role: Lilly, Immune Design, Merck Serono, Adaptimmune, Daiichi Sankyo, Eisai, Morphotek, TRACON Pharma, Immodulon Therapeutics, Deciphera, PharmaMar, Blueprint Medicines, Clinigen Group, Epizyme, Boehringer Ingelheim, Bayer, Karma Oncology, UpToDate, Athenex, Immunicum, Mundipharma, SpringWorks Therapeutics, SynOX
Research Funding: GlaxoSmithKline (Inst)
Travel, Accommodations, Expenses: PharmaMar

Albiruni Abdul Razak
Consulting or Advisory Role: Adaptimmune, Bayer, GlaxoSmithKline, Medison, Inhibrx
Research Funding: Deciphera, Karyopharm Therapeutics, Pfizer, Roche/Genentech, Bristol Myers Squibb, MedImmune, Amgen, GlaxoSmithKline, Blueprint Medicines, Merck, AbbVie, Adaptimmune, Iterion Therapeutics, Neoleukin Therapeutics, Daiichi Sankyo, Symphogen, Rain Therapeutics
Expert Testimony: Medison

Suzanne George
Stock and Other Ownership Interests: Abbott Laboratories
Honoraria: CStone Pharmaceuticals
Consulting or Advisory Role: Blueprint Medicines, Deciphera, Bayer, Lilly, UpToDate, Research to Practice, MORE Health, Daiichi, Kayothera, Immunicum
Research Funding: Blueprint Medicines (Inst), Deciphera (Inst), Daiichi Sankyo RD Novare (Inst), Merck (Inst), Eisai (Inst), SpringWorks Therapeutics (Inst), TRACON Pharma (Inst), Theseus Pharmaceuticals (Inst), BioAtla
Patents, Royalties, Other Intellectual Property: UptoDate
Expert Testimony: Bayer
Other Relationship: Research to Practice, WCG

Axel Le Cesne
Honoraria: Bayer, PharmaMar, Deciphera

Michael C. Heinrich
Honoraria: Novartis
Consulting or Advisory Role: Novartis, Blueprint Medicines, Deciphera, Theseus Pharmaceuticals
Patents, Royalties, Other Intellectual Property: Patent on treatment of GIST-licensed to Novartis (Inst)

Patrick Schöffski
Honoraria: Blueprint Medicines
Consulting or Advisory Role: Deciphera, Ellipses Pharma, Blueprint Medicines, Transgene, Exelixis, Boehringer Ingelheim, Studiecentrum voor Kernenergie (SCK CEN), SQZ Biotechnology, Adcendo, PharmaMar, Merck, Medpace
Research Funding: CoBioRes NV (Inst), Eisai (Inst), G1 Therapeutics (Inst), PharmaMar (Inst), Genmab (Inst), Merck (Inst), Sartar Therapeutics (Inst), ONA Therapeutics (Inst)

Ying Su
Employment: Codiak Biosciences, Deciphera
Stock and Other Ownership Interests: Deciphera, Codiak Biosciences

Margaret von Mehren
Consulting or Advisory Role: Deciphera, GlaxoSmithKline
Research Funding: Novartis (Inst), Deciphera (Inst), Gradalis (Inst), Genmab (Inst), ASCO (Inst), Solaris Health (Inst)
Patents, Royalties, Other Intellectual Property: Cell line
Other Relationship: NCCN

Hans Gelderblom
Research Funding: Novartis (Inst), Ipsen (Inst), Deciphera (Inst), Daiichi (Inst)

Steven Attia
Research Funding: AB Science (Inst), TRACON Pharma (Inst), Bayer (Inst), Novartis (Inst), Lilly (Inst), Immune Design (Inst), Karyopharm Therapeutics (Inst), Epizyme (Inst), Blueprint Medicines (Inst), Genmab (Inst), CBA Pharma (Inst), Desmoid Tumor Research Foundation, Merck (Inst), Philogen (Inst), Gradalis (Inst), Deciphera (Inst), Takeda (Inst), Incyte (Inst), SpringWorks Therapeutics (Inst), Adaptimmune (Inst), Advenchen Laboratories (Inst), Bavarian Nordic (Inst), BTG (Inst), PTC Therapeutics (Inst), GlaxoSmithKline (Inst), FORMA Therapeutics (Inst), TRACON Pharma (Inst), Ayala Pharmaceuticals (Inst), Trillium Therapeutics (Inst), Boehringer Ingelheim (Inst), Salarius Pharmaceuticals (Inst), Theseus Pharmaceuticals (Inst), Monopar Therapeutics (Inst), C4 Therapeutics (Inst), InhibRx (Inst), Noxopharm (Inst), Rain Therapeutics (Inst)

Rodrigo Ruiz-Soto
Employment: Deciphera
Stock and Other Ownership Interests: Deciphera, Immunogen
Patents, Royalties, Other Intellectual Property: I am an inventor in three patents with Immunogen, I transferred the rights to Immunogen. I have not received (and I will not receive) any royalties, I am an inventor in pending patents at Deciphera. I have transferred the rights to Deciphera, I have not received (and will not receive) any royalties

John R. Zalcberg
Leadership: ICON Group
Stock and Other Ownership Interests: Biomarin, Opthea, Amarin Corporation, Concert Pharmaceuticals, Frequency Therapeutics, Gilead Sciences, Madrigal Pharmaceuticals, UniQure, Zogenix, Orphazyme, Moderna Therapeutics, Twist Bioscience, Novavax
Honoraria: Specialised Therapeutics, Merck Serono, Targovax, Halozyme, Gilead Sciences, Deciphera
Consulting or Advisory Role: Merck Serono, Targovax, Merck Sharp & Dohme, Halozyme, Lipotek, Specialised Therapeutics, Center for Emerging & Neglected Diseases (CEND), Deciphera, REVOLUTION MEDICINE, FivePHusion, Genor BioPharma, 1Globe Health Institute, Novotech
Research Funding: Merck Serono (Inst), Bristol Myers Squibb (Inst), AstraZeneca (Inst), Pfizer (Inst), IQvia (Inst), Mylan (Inst), Ipsen (Inst), Eisai (Inst), Medtronic (Inst), MSD Oncology (Inst)
Travel, Accommodations, Expenses: Merck Serono, AstraZeneca, Merck Sharp & Dohme, Deciphera, Sanofi

Julie Meade
Employment: Deciphera, Mirati Therapeutics
Stock and Other Ownership Interests: Deciphera, Mirati Therapeutics
Travel, Accommodations, Expenses: Deciphera, Mirati Therapeutics

Jean-Yves Blay
Leadership: Innate Pharma
Honoraria: Roche, AstraZeneca, PharmaMar, MSD, BMS, Bayer, Ignyta, Deciphera
Consulting or Advisory Role: Roche, Pharmamar, Blueprint Medicines, Bayer, Deciphera, Karyopharm Therapeutics
Research Funding: GlaxoSmithKline (Inst), Pharmamar (Inst), Novartis (Inst), Bayer (Inst), Roche (Inst), BMS (Inst), MSD (Inst), DEciphera (Inst), AstraZeneca (Inst), OSE Pharma (Inst)
Travel, Accommodations, Expenses: Roche

Jonathan Trent
Consulting or Advisory Role: Blueprint Medicines, Deciphera, Daiichi Sankyo, Epizyme, Agios, C4 Therapeutics, Bayer, AADI Bioscience, LLC, Foghorn Therapeutics, Boehringer Ingelheim, Cogent Medicine, SERVIER

Matthew L. Sherman
Employment: Deciphera, Pieris Pharmaceuticals
Leadership: Deciphera, Pieris Pharmaceuticals
Stock and Other Ownership Interests: Deciphera, Pieris Pharmaceuticals

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Study Investigators and Investigational Sites

Principal Investigator	Institution	Country
Suzanne George	Dana-Farber Cancer Institute	United States
Michael C. Heinrich	Oregon Health and Science University	United States
Kristen Ganjoo	Stanford University Medical Center	United States
Rodolfo Bordoni	Georgia Cancer Specialists	United States
Hedy Kindler	University of Chicago Medical Center	United States
Arun Singh	UCLA Medical Center	United States
Margaret von Mehren	Fox Chase Cancer Center	United States
Ping Chi	Memorial Sloan Kettering Cancer Center	United States
Neeta Somaiah	University of Texas MD Anderson Cancer Center	United States
Steven Attia	Mayo Clinic in Florida	United States
Keith Skubitz	University of Minnesota Hospital	United States
Brittany Siontis	Mayo Clinic	United States
Aparna Kalyan	Northwestern Center for Clinical Research	United States
Richard Riedel	Duke University Medical Center	United States
Hari Deshpande	Yale Cancer Center	United States
Gabriel Tinoco	The Ohio State University Comprehensive Cancer Center	United States
Jonathan Trent	University of Miami Miller School of Medicine	United States
Adam Burgoyne	University of California San Diego Medical Center	United States
Jennifer Chuy	Montefiore Medical Center	United States
Sagila George	Oklahoma University Health Sciences Center	United States
Vicki Keedy	Vanderbilt University Medical Center	United States
Christian Meyer	Johns Hopkins University School of Medicine	United States
Roland Skeel	University of Toledo	United States
Daniel Rushing	Indiana University Simon Cancer Center	United States
Brian Van Tine	Washington University	United States
Sosipatros Boikos	Massey Cancer Center	United States
Ira Wollner	Henry Ford Medical Center	United States
John Charlson	Medical College of Wisconsin Inc	United States
Varun Monga	University of Iowa Hospital and Clinics	United States
Tony Philip	The Monter Cancer Center	United States
Santiago Aparo	Baptist Health Medical Group Oncology, LLC	United States
Allen Cohn	Rocky Mountain Cancer Centers	United States
Andrew Paulson	Baylor Charles A. Sammons Cancer Center	United States
Michael Wagner	University of Washington	United States
Mahesh Seetharam	Mayo Clinic Arizona	United States
Mihaela Druta	Moffitt Cancer Center	United States
Albiruni Abdul Razak	Princess Margaret Cancer Center	Canada
Karen Mulder	Cross Cancer Institute	Canada
Jonathan Noujaim	Hôpital Maisonneuve-Rosemont	Canada
Kevin Zbuk	Juravinski Cancer Clinic	Canada

(continued on following page)

TABLE A1. Study Investigators and Investigational Sites (continued)

Principal Investigator	Institution	Country
John Zalcberg	The Alfred Hospital	Australia
David Goldstein	Prince of Wales Hospital	Australia
Vladimir Andelkovic	Princess Alexandra Hospital	Australia
Sarwan Bishnoi	Ashford Cancer Centre Research	Australia
Craig Underhill	Border Medical Oncology Research Unit	Australia
Nagavalli Somasundaram	National Cancer Centre	Singapore
Li-Yuan Bai	China Medical University Hospital	Taiwan
Chia-Jui Yen	National Cheng Kung University Hospital	Taiwan
Chun-Nan Yeh	Chang Gung Memorial Hospital, Linkou	Taiwan
Chueh-Chuan Yen	Taipei Veterans General Hospital	Taiwan
Yen-Hao Chen	Kaohsiung Chang Gung Memorial Hospital	Taiwan
Yoon-Koo Kang	Asan Medical Center	Korea
Seok Yun Kang	Ajou University Hospital	Korea
Joon Oh Park	Samsung Medical Center	Korea
Tae-Yong Kim	Seoul National University Hospital	Korea
Jean-Yves Blay	Centre Léon Bérard	France
Axel Le Cesne	Gustave Roussy	France
Antoine Italiano	Institut Bergonié	France
Francois Bertucci	Institut Paoli Calmettes	France
Emmanuelle Bompas	ICO—Site René Gauducheau	France
Florence Duffaud	Hôpital de la Timone	France
Nicolas Penel	Centre Oscar Lambret	France
Alice Hervieu	Centre Georges François Leclerc	France
Nicolas Isambert	CHU de Poitiers	France
Zsuzsanna Papai	Magyar Honvedseg Egeszsegugyi Kozpont	Hungary
Peter Arkosy	Debreceni Egyetem	Hungary
Sebastian Bauer	Universitaetsklinikum Essen	Germany
Peter Reichardt	HELIOS Klinikum Berlin-Buch	Germany
Stephan Richter	Universitaetsklinikum Carl Gustav Carus TU Dresden	Germany
Christina Linder Stragliotto	Karolinska universitetssjukhuset - Solna	Sweden
Elena Fumagalli	Fondazione IRCCS Istituto Nazionale dei Tumori	Italy
Bruno Vincenzi	Università Campus Bio-Medico di Roma	Italy
Antonella Brunello	IOV - Istituto Oncologico Veneto IRCCS	Italy
Giovanni Grignani	Fondazione del Piemonte per l'Oncologia IRCC Candiolo	Italy
Maria Pantaleo	Azienda Ospedaliera Universitaria Policlinico Sant'Orsola Malpighi	Italy
Giuseppe Badalamenti	A.O.U.P. "Paolo Giaccone"	Italy
Christian Britschgi	Universitaetsspital Zuerich	Switzerland
Hans Gelderblom	Leids Universitair Medisch Centrum	Netherlands
Ingrid Desar	Radboudumc	Netherlands
An Reyners	Universitair Medisch Centrum Groningen (UMCG)	Netherlands
Neeltje Steeghs	Antoni van Leeuwenhoek	Netherlands
Kjetil Boye	Oslo University Hospital	Norway
Piotr Rutkowski	Narodowy Instytut Onkologii	Poland

(continued on following page)

TABLE A1. Study Investigators and Investigational Sites (continued)

Principal Investigator	Institution	Country
Cesar Serrano Garcia	Hospital Universitari Vall d'Hebron	Spain
Pilar Sancho Marquez	Hospital Universitario Virgen del Rocio	Spain
Virginia Martínez-Marín	Hospital Universitario La Paz	Spain
Maria Angeles Vaz Salgado	Hospital Universitario Ramon y Cajal	Spain
Javier Lavernia Giner	Instituto Valenciano de Oncologia IVO	Spain
Antonio Cubillo Gracian	Hospital Universitario HM Madrid Sanchinarro	Spain
Josefina Cruz Jurado	Hospital Universitario de Canarias	Spain
Antonio Lopez Pousa	Hospital de la Santa Creu i Sant Pau	Spain
Maria Angeles Sala Gonzalez	Hospital de Basurto	Spain
Juan Antonio Carrasco Alvarez	Complejo Hospitalario Universitario de Vigo	Spain
Isabel Sevilla Garcia	Hospital Clinico Universitario Virgen de la Victoria	Spain
Antonio Casado Herraez	Hospital Clinico San Carlos	Spain
Robin Jones	Royal Marsden Hospital	United Kingdom
Jeffery White	Beatson West of Scotland Cancer Centre	United Kingdom
Daniel Stark	St James's University Hospital	United Kingdom
Palma Dileo	University College London Hospitals	United Kingdom
Ofer Merimsky	Tel Aviv Sourasky Medical Center	Israel
Nirit Yarom	Assaf Harofeh	Israel
Patrick Schöffski	UZ Leuven	Belgium
Thierry Gil	Institut Jules Bordet	Belgium
Matias Chacon	Instituto Medico Especializado Alexander Fleming	Argentina
Gustavo Jarchum	Sanatorio Allende	Argentina
Cesar Sanchez	Centro de Cáncer—Hospital Clínico Pontificia Universidad Católica de Chile	Chile

NOTE. Sites listed here are those that screened a patient for the INTRIGUE trial.