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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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; nominal 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% vs 14.6%, nominal P = .03). Ripretinib was associated with a more favorable safety profile, fewer grade 3/4 treatment-emergent adverse events (41.3% vs 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.

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 (PDGFRα).1-5 First-line treatment with imatinib—a KIT and PDGFRα 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.13-14 Given the heterogeneous nature of KIT and PDGFRα 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 PDGFRα activity.16 It is approved for the treatment of patients with advanced GIST who...
received prior treatment with three or more TKIs, including imatinib, on the basis of the results of the phase III INVICTUS study.\textsuperscript{17,18} Phase I data suggest ripretinib is effective as second-line therapy in patients with advanced GIST (median PFS: 10.7 months).\textsuperscript{19} Ripretinib had higher activity against imatinib-resistant secondary \(\textbf{KIT}\) mutations in vitro versus sunitinib, suggesting that ripretinib may be superior in second-line GIST.\textsuperscript{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.\textsuperscript{20,21} INTRIGUE was active at 122 sites in 22 countries. Patients were stratified by mutational status (\(\textbf{KIT}\) exon 11, \(\textbf{KIT}\) exon 9, \(\textbf{KIT}/\textbf{PDGFRA}\) wild-type [WT], and other \(\textbf{KIT}\) [other than exon 9 or exon 11]/\(\textbf{PDGFRA}\) 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 \(\geq\) 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\textsuperscript{22}) within 21 days before administration of study drug, provided an archival tissue sample and pathology report containing \(\textbf{KIT}/\textbf{PDGFRA}\) 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) \# 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 \(\textbf{KIT}\) 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...
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

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### 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. 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. 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,* 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*                       | 17 (7.5)             | 16 (7.0)            | 33 (7.3)        |
| Imatinib intolerance,* 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.

*On the basis of interactive response technology stratification.

*Other KIT included any patient with a KIT mutation other than exon 9 or exon 11.
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 vs 7.0 months; Fig 2A) or ITT population (HR, 1.05; 95% CI, 0.82 to 1.33; nominal P = .72 at the data cutoff (September 1, 2021). Similar results were observed in sensitivity analyses.

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

| Parameter | KIT Exon 11 ITT Population | ITT Population |
|-----------|-----------------------------|----------------|
| ORR, No. (%) | Ripretinib (n = 163) | Sunitinib (n = 164) | Ripretinib (n = 226) | Sunitinib (n = 227) |
| 95% CI | 39 (23.9) | 24 (14.6) | 49 (21.7) | 40 (17.6) |
| CR, No. (%) | 17.6 to 31.2 | 9.6 to 21.0 | 16.5 to 27.6 | 12.9 to 23.2 |
| PR, No. (%) | 0 | 2 (1.2) | 1 (0.4) | 3 (1.3) |
| Difference in ORR, % (95% CI) | 9.3 (0.7 to 17.8) | 4.2 (–3.2 to 11.5) |
| P< | .03 | .27 |

DOR, months, median (95% CI)
- Ripretinib: 16.7 (12.5 to NE)
- Sunitinib: 20.1 (11.0 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.

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

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

*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                     | 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, No. (%)                    | 44 (19.7)             | 111 (50.2)          |
| Any dose interruption, No. (%)                 | 62 (27.8)             | 84 (38.0)           |
| Sunitinib dose regimen modification, No. (%)   |                       |                     |
| No                                             | NA                    | 174 (78.7)          |
| Yes                                            | NA                    | 47 (21.3)           |
| Continuous dosing                              | NA                    | 33 (14.9)           |
| Other                                          | NA                    | 19 (8.6)            |
| Any TEAE, No. (%)                              | 221 (99.1)            | 219 (99.1)          |
| Any grade 3/4 TEAE                             | 92 (41.3)             | 145 (65.6)          |
| Any grade 3/4 drug-related TEAE                | 211 (94.6)            | 214 (96.8)          |
| Any treatment-emergent SAE, No. (%)            | 59 (26.5)             | 122 (55.2)          |
| Any drug-related treatment-emergent SAE        | 57 (25.6)             | 57 (25.8)           |
| 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.

*Modification from the standard 4 weeks on/2 weeks off schedule.

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.

Ripretinib was generally well tolerated and its safety profile was consistent with existing prescribing information (Table 3). 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). 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% vs. 26.7%), neutropenia or neutrophil count decreased (0% vs. 13.1%), PPES (1.3% vs. 10%), diarrhea (0.9% vs. 2.7%), hypertriglyceridemia (0.4% vs. 3.2%), lymphocyte count decreased (0.4% vs. 2.3%), and stomatitis (0% vs. 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
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: 28.7 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. 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). In that trial, efficacy end points were evaluated using RECIST, not mRECIST v1.1. 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]). 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. 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. 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. Ripretinib demonstrated good tolerability across all mutation types;

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

| Preferred Term               | Ripretinib (n = 223) | Sunitinib (n = 221) |
|------------------------------|----------------------|---------------------|
|                              | All Grades, No. (%)  | Grade 3/4, No. (%)  | All Grades, No. (%)  | Grade 3/4, No. (%)  |
| Alopexia                     | 143 (64.1)           | NA                  | 18 (8.1)            | NA                  |
| 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.

*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.

**The highest-grade severity for alopecia is grade 2.
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.  

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.

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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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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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For more information about ASCO’s conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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

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No other potential conflicts of interest were reported.
## 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 Sionsis       | 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    |
| Sospipatos 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                    | United States    |
| Karen Mulder           | Cross Cancer Institute                            | Canada           |
| Jonathan Noujaim       | Hôpital Maisonneuve-Rosemont                      | Canada           |
| Kevin Zbuk             | Juravinski Cancer Clinic                          | Canada           |

(continued on following page)
| Principal Investigator          | Institution                                                                 | Country   |
|--------------------------------|------------------------------------------------------------------------------|-----------|
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| 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    |
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| Peter Arkosy                  | Debreceni Egyetem                                                           | Hungary   |
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| Giuseppe Badalamenti          | A.O.U.P. “Paolo Giaccone”                                                    | Italy     |
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| 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)
| Principal Investigator                  | Institution                                                        | Country   |
|----------------------------------------|--------------------------------------------------------------------|-----------|
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| Pilar Sancho Marquez                   | Hospital Universitario Virgen del Rocio                            | Spain     |
| Virginia Martinez-Marin                | 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     |
| Josefin 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     |
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| Jeffery White                          | Beatson West of Scotland Cancer Centre                             | United Kingdom |
| Daniel Stark                           | St James’s University Hospital                                      | United Kingdom |
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NOTE. Sites listed here are those that screened a patient for the INTRIGUE trial.