# Patient-reported outcomes and tolerability in patients receiving ripretinib versus sunitinib after treatment with imatinib in INTRIGUE, a phase 3, open-label study1

Gelderblom, H.; Jones, R.L.; Blay, J.Y.; George, S.; Mehren, M. von; Zalcberg, J.R.; ... ; Bauer, S.

European Journal of Cancer 192 (2023) 113245

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

# Patient-reported outcomes and tolerability in patients receiving ripretinib versus sunitinib after treatment with imatinib in INTRIGUE, a phase 3, open-label study[1]

Hans Gelderblom [a], Robin L. Jones [b], Jean-Yves Blay [c], Suzanne George [d], Margaret von Mehren [e], John R. Zalcberg [f], Yoon-Koo Kang [g], Albiruni Abdul Razak [h], Jonathan Trent [i], Steven Attia [j], Axel Le Cesne [k], Brittany L. Siontis [l], David Goldstein [m], Kjetil Boye [n], Cesar Sanchez [o], Neeltje Steeghs [p], Piotr Rutkowski [q], Mihaela Druta [r], César Serrano [s], Neeta Somaiah [t], Ping Chi [u], Brooke Harrow [v,*], Claus Becker [v], William Reichmann [v], Matthew L. Sherman [v], Rodrigo Ruiz-Soto [v], Michael C. Heinrich [w], Sebastian Bauer [x,y], on behalf of the INTRIGUE investigators

[a] *Leiden University Medical Center, Leiden, the Netherlands*
[b] *Royal Marsden Hospital and Institute of Cancer Research, London, UK*
[c] *Centre Léon Bérard and University Claude Bernard Lyon 1, Lyon, France*
[d] *Dana-Farber Cancer Institute, Boston, MA, USA*
[e] *Fox Chase Cancer Center, Philadelphia, PA, USA*
[f] *Department of Medical Oncology, Alfred Health and School of Public Health, Monash University, Melbourne, Australia*
[g] *Asan Medical Center, University of Ulsan, Seoul, Korea*
[h] *Princess Margaret Cancer Centre, Toronto, ON, Canada*
[i] *Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, USA*
[j] *Mayo Clinic, Jacksonville, FL, USA*
[k] *Gustave Roussy, Vellejuif, France*
[l] *Mayo Clinic, Rochester, MN, USA*
[m] *Prince of Wales Hospital and Clinical School University of New South Wales, New South Wales, Australia*
[n] *Department of Oncology, Oslo University Hospital, Oslo, Norway*
[o] *Department of Hematology and Oncology, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile*
[p] *Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, the Netherlands*
[q] *Maria Sklodowska-Curie National Research Institute of Oncology, Warszawa, Poland*
[r] *Moffit Cancer Center, Tampa, FL, USA*
[s] *Vall d'Hebron Institute of Oncology, Barcelona, Spain*
[t] *MD Anderson Cancer Center, Houston, TX, USA*
[u] *Memorial Sloan Kettering Cancer Center, New York, NY, USA*
[v] *Deciphera Pharmaceuticals, LLC, Waltham, MA, USA*

[1] Trial registration: NCT03673501.

[*] *Corresponding author:* Deciphera Pharmaceuticals, LLC, 200 Smith Street, Waltham, MA 02451, USA.
*E-mail address:* brooke.harrow@deciphera.com (B. Harrow).

https://doi.org/10.1016/j.ejca.2023.113245

[w] Portland VA Healthcare System and Knight Cancer Institute, Oregon Health and Science University, Portland, OR, USA
[x] Department of Medical Oncology and Sarcoma Center at the West German Cancer Center, University Hospital Essen, Essen, Germany
[y] German Cancer Consortium (DKTK), Partner Site University Hospital Essen, Essen, Germany

Received 17 April 2023; Received in revised form 5 July 2023; Accepted 8 July 2023
Available online 20 July 2023

**KEYWORDS**
Gastrointestinal stromal tumours;
Patient reported outcome measures;
Quality of life;
Protein kinase inhibitors

**Abstract** ***Purpose:*** In the INTRIGUE trial, ripretinib showed no significant difference versus sunitinib in progression-free survival for patients with advanced gastrointestinal stromal tumour (GIST) previously treated with imatinib. We compared the impact of these treatments on health-related quality of life (HRQoL).
***Patients and methods:*** Patients were randomised 1:1 to once-daily ripretinib 150 mg or once-daily sunitinib 50 mg (4 weeks on/2 weeks off). Patient-reported outcomes were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer-30 (EORTC QLQ-C30) questionnaire at day (D)1, and D29 of all cycles until treatment discontinuation. Change from baseline was calculated. Time without symptoms or toxicity (TWiST) was estimated as the mean number of days without progression, death, or grade ≥3 treatment-emergent adverse events per patient over 1 year of follow-up.
***Results:*** Questionnaire completion at baseline was 88.1% (199/226) for ripretinib and 87.7% (199/227) for sunitinib and remained high for enrolled patients throughout treatment. Patients receiving sunitinib demonstrated within-cycle variation in self-reported HRQoL, corresponding to the on/off dosing regimen. Patients receiving ripretinib reported better HRQoL at D29 assessments than patients receiving sunitinib on all scales except constipation. HRQoL was similar between treatments at D1 assessments, following 2 weeks without treatment for sunitinib patients. TWiST was greater for ripretinib patients (173 versus 126 days).
***Conclusion:*** Patients receiving ripretinib experienced better HRQoL than patients receiving sunitinib during the dosing period and similar HRQoL to patients who had not received sunitinib for 2 weeks for all QLQ-C30 domains except constipation. Ripretinib may provide clinically meaningful benefit to patients with advanced GIST previously treated with imatinib.


## 1. Introduction

Gastrointestinal stromal tumour (GIST) is the most common sarcoma of the gastrointestinal tract [1–3]. About 90% of these cases are driven by gain-of-function mutations in *KIT* or platelet-derived growth factor α (*PDGFRA*) [3].

Tyrosine kinase inhibitors (TKI) that target *KIT* and *PDGFRA* mutations are approved for the treatment of patients with GIST [3–5]. Initial disease control and tumour response is often achieved with first-line treatment with imatinib, a KIT and PDGFRA TKI, although about 50% of patients show resistance to imatinib after 2 years [3,4,6]. Sunitinib, a multitargeted TKI, is approved as the second-line treatment [7,8], and the third-line treatment consists of the multi-kinase inhibitor regorafenib [9]. The fourth-line treatment of patients with advanced GIST consists of ripretinib, a switch-control TKI with inhibition of KIT and PDGFRA activity [10–12].

While treatment options have extended the overall survival (OS) and progression-free survival (PFS) of patients with GIST, patients may experience side effects of treatment that impact their physical health and quality of life. Treatment tolerability and the health-related quality of life (HRQoL) of patients on treatment have therefore become increasingly relevant and should be considered when determining clinical benefit [13–18]. Recognition of these factors has grown among regulatory agencies such as the Food and Drug Administration [19], as well as within international societies and professional organisations [18,20].

Among available treatments for GIST, imatinib is generally well tolerated, but patients receiving sunitinib and regorafenib report a comparatively large decrease in HRQoL [9,14,15,21]. Patients receiving these treatments often require dose reductions and regimen changes to manage toxicity [21,22]. In the phase 3 INVICTUS trial, patients receiving ripretinib maintained HRQoL on

patient-reported outcome (PRO) measures compared with patients receiving placebo [10,23].

INTRIGUE, a phase 3, interventional, randomised, global, multicentre, open-label trial evaluated ripretinib versus sunitinib for the treatment of patients with advanced GIST who were previously treated with or intolerant to imatinib. Median PFS for ripretinib and sunitinib among the *KIT* exon 11 primary mutation group was 8.3 and 7.0 months, respectively (hazard ratio [HR]: 0.88; 95% confidence interval [CI]: 0.66, 1.16; p = 0.36). Among all patients in the intention-to-treat (ITT) population, PFS was 8.0 and 8.3 months for patients receiving ripretinib versus sunitinib, respectively (HR: 1.05; 95% CI: 0.82, 1.33; nominal p = 0.72) [24]. The INTRIGUE trial did not meet its primary endpoint of superiority in PFS of ripretinib over sunitinib in second-line patients with advanced GIST [24]. However, ripretinib had a more favourable safety and tolerability profile than sunitinib, with fewer grade 3 or 4 treatment-emergent adverse events (TEAEs; 41.3% versus 65.6%; nominal p < 0.0001) [24]. Due to these findings, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for GIST version 1.2023 now recommend the consideration of ripretinib for patients intolerant of second-line sunitinib treatment [25].

In this analysis of the INTRIGUE trial, we evaluated the impact of ripretinib and sunitinib on patient HRQoL in patients with advanced GIST using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer-30 (QLQ-C30), a commonly used PRO measure in this population [14,15,26].

The patient experience of treatment toxicity and efficacy can also be summarised through a time without symptoms or toxicity (TWiST) analysis, which divides time prior to progression into two health states, thereby evaluating the tradeoff between treatment toxicity and efficacy [27]. To further explore the tolerability benefit between the two arms, we performed a TWiST analysis for patients receiving ripretinib or sunitinib in the INTRIGUE trial.

## 2. Methods

### 2.1. Patients and study design

The study design for INTRIGUE (NCT03673501) has been described previously [24]. In brief, patients were stratified by primary mutational status and imatinib intolerance and were subsequently randomised 1:1 to continuous ripretinib 150 mg once daily (QD) or sunitinib 50 mg QD 4 weeks on/2 weeks off, ongoing in 6-week cycles until discontinuation. Dose modification was allowed per the package insert for patients receiving sunitinib or per protocol toxicity management guidelines for patients receiving ripretinib [24]. The primary endpoint of the INTRIGUE trial was PFS, and HRQoL was assessed as a secondary endpoint [24].

This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by an institutional review board or ethics committee at each site and by appropriate regulatory authorities. Patients provided written informed consent.

### 2.2. Study procedures and evaluations

Assessments for tumour response and adverse events have been previously described [24].

### 2.3. PRO assessments

The QLQ-C30 was used to assess the HRQoL of all patients in the ITT population [26,28]. HRQoL assessments were completed using an electronic PRO system at baseline, day (D) 15 and D29 (± 1 day) of cycle (C)1, as well as D1 and D29 (± 3 days) of every cycle thereafter, and within a week following end of treatment (Fig. 1). From C3 D29, patients completed PRO assessments at home.

### 2.4. Statistical analysis

QLQ-C30 scores were calculated according to the QLQ-C30 manual [29]. Patients in the ITT population with

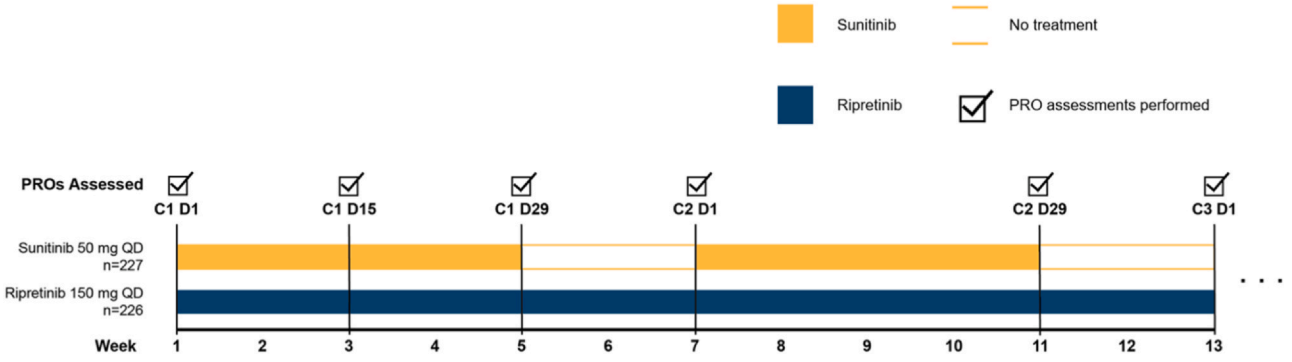



Fig. 1. Study design and PRO assessment schedule. C, cycle; D, day; PRO, patient-reported outcome; QD, once daily.

baseline and post-baseline values available were included. Summary statistics and confidence intervals are reported. Minimum clinically important differences (MCIDs) for most scales of the QLQ-C30 are not established in patients with advanced GIST. Accordingly, MCIDs for each multi-item or single-item scale were estimated using one half of a standard deviation of responses at baseline per the approach of Norman et al [30].

During the 365-day period used for the post-hoc TWiST analysis, time was partitioned into one of three states: toxicity (TOX), relapse (REL), and TWiST (Supplemental Fig. S1). Restricted mean survival time (RMST) was calculated as the area under the survival curve for each state. TOX was defined as days prior to progression with any grade ≥3 TEAE, regardless of relation to treatment, from randomisation to progression/censoring, calculated by subtracting the end date from the start date of the TEAE. Days with overlapping TEAEs were counted only once. If TOX was ongoing, the number of days was censored at the minimum of progression date, day 365, safety follow-up date, or last dose date plus 30 days. Sensitivity analyses were performed defining TOX as days with grade ≥2 TEAEs. REL was defined as the period after disease progression, including all days after the date of progression until death or censoring. Progression after day 365 was considered as censored at day 365. TWiST was therefore defined as the time spent alive, pre-progression, without grade ≥3 TEAEs, calculated by subtracting the mean days spent in TOX from the mean PFS [27]. A post-hoc quality-adjusted TWiST (Q-TWiST) analysis was also performed. Standardised weights of 0.5, 0.5, and 1, for TOX, REL, and TWiST, respectively, were used. Sensitivity analyses were performed [31].

## 3. Results

### 3.1. Patient disposition and baseline characteristics

Overall, 453 patients were randomly assigned to receive ripretinib 150 mg QD (n = 226) or sunitinib 50 mg QD on a 4 weeks on/2 weeks off schedule (n = 227; Supplemental Fig. S2). Baseline characteristics, which have been previously reported [24], and mean baseline patient HRQoL, as measured by QLQ-C30 scores (Table 1), were similar between the two treatment arms.

### 3.2. EORTC QLQ-C30

Completion of the QLQ-C30 questionnaire was high at baseline for patients in the ITT set in both the ripretinib arm (199/226; 88.1%) and the sunitinib arm (199/227; 87.7%) and remained high for enrolled patients throughout treatment across both arms (Supplemental Fig. S3). After C8 D1, fewer than 25% of randomised patients were eligible to complete the questionnaires due to treatment discontinuation.

Table 1
Mean baseline EORTC QLQ-C30 scores.

| Baseline characteristic | Ripretinib (n = 199) | Sunitinib (n = 199) | MCID[a] |
|---|---|---|---|
| Global Health Status,[b] mean (SD) | 74.9 (19.7) | 73.5 (19.3) | 9.8 |
| *EORTC QLQ-C30 functioning scales,[b] mean (SD)* | | | |
| Role functioning | 86.9 (21.6) | 88.4 (20.7) | 10.6 |
| Physical functioning | 87.6 (16.4) | 86.8 (15.9) | 8.1 |
| Emotional functioning | 80.7 (19.2) | 81.1 (18.4) | 9.4 |
| Social functioning | 91.0 (18.1) | 91.2 (16.9) | 8.7 |
| Cognitive functioning | 90.1 (17.9) | 92.5 (12.5) | 7.6 |
| *EORTC QLQ-C30 symptom scales,[c] mean (SD)* | | | |
| Fatigue | 24.2 (24.0) | 23.6 (22.5) | 11.6 |
| Pain | 18.3 (21.8) | 17.8 (21.4) | 10.8 |
| Appetite loss | 14.2 (21.5) | 12.6 (22.3) | 11.0 |
| Nausea and vomiting | 5.4 (12.7) | 4.7 (10.7) | 5.9 |
| Diarrhoea | 10.2 (20.1) | 9.9 (17.3) | 9.4 |
| Constipation | 10.6 (20.8) | 11.9 (21.4) | 10.6 |
| Insomnia | 18.3 (25.2) | 20.1 (26.3) | 12.9 |
| Dyspnoea | 9.7 (18.8) | 10.4 (19.3) | 9.5 |
| Financial difficulties | 9.9 (21.7) | 6.9 (17.2) | 9.7 |

EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer-30; ITT, intention-to-treat; MCID, minimum clinically important difference; SD, standard deviation; QoL, quality of life.

[a] MCIDs were calculated as one half of the mean standard deviation of the two treatment arms at baseline based on all patients in the ITT population with evaluable baseline data.

[b] For functioning scales and global health status, scores are reported out of 100, and a high score represents a higher level of functioning, corresponding to higher QoL.

[c] For symptom scales, a high score represents higher levels of symptomatology, corresponding to lower QoL.

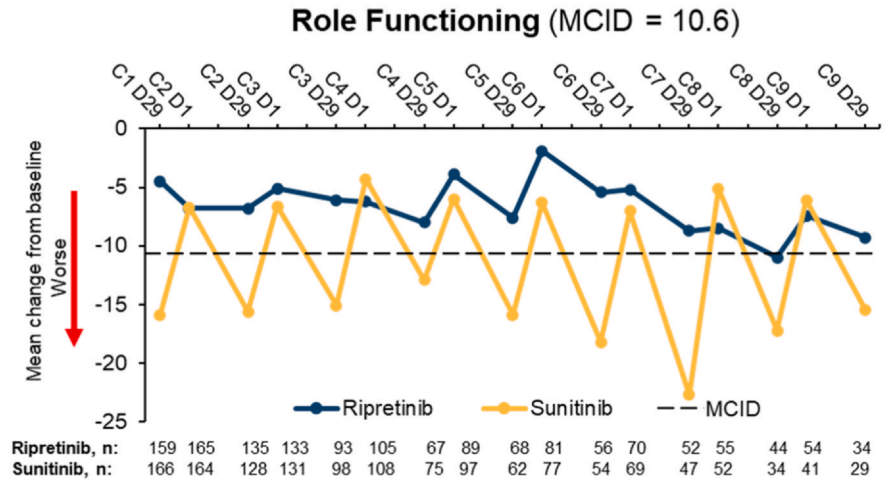
Across treatment cycles, patients receiving sunitinib reported cyclical variation on most PRO measures as indicated by QLQ-C30 scores. Patients receiving sunitinib reported less impact on functional domains and symptom domains on D1 assessments, which followed the 2-week period without daily sunitinib treatment, compared with D29 assessments, which followed 4 weeks of daily sunitinib treatment (Fig. 2A–C; Supplemental Fig. S4). Ripretinib QLQ-C30 scores did not demonstrate substantial cyclical variation.

#### 3.2.1. Functional scales

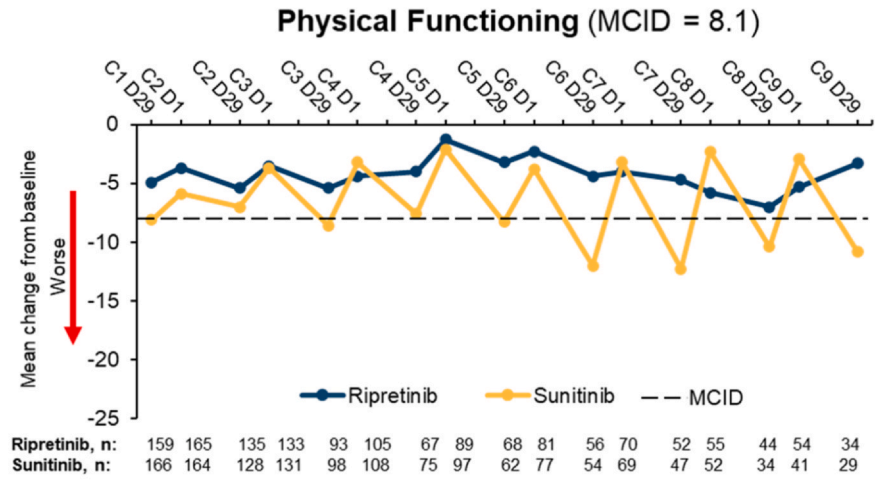
Patients receiving ripretinib generally reported better outcomes than patients receiving sunitinib across functional scales. At multiple assessments, patients receiving ripretinib reported significantly less decline from baseline in role functioning and physical functioning compared to patients receiving sunitinib (Fig. 3A; Supplemental Fig. S5A).

Average deterioration from baseline QLQ-C30 role functioning and physical functioning rarely exceeded the MCID for patients receiving ripretinib across the first nine cycles (54 weeks) of treatment for both D1 and D29 assessments. Patients receiving ripretinib and sunitinib generally experienced similar deterioration

A.


Role Functioning (MCID = 10.6)
C1 D29 C2 D1 C2 D29 C3 D1 C3 D29 C4 D1 C4 D29 C5 D1 C5 D29 C6 D1 C6 D29 C7 D1 C7 D29 C8 D1 C8 D29 C9 D1 C9 D29
0 -5 -10 -15 -20 -25
Mean change from baseline
Worse
Ripretinib Sunitinib MCID
Ripretinib, n: 159 165 135 133 93 105 67 89 68 81 56 70 52 55 44 54 34
Sunitinib, n: 166 164 128 131 98 108 75 97 62 77 54 69 47 52 34 41 29

B.


Physical Functioning (MCID = 8.1)
C1 D29 C2 D1 C2 D29 C3 D1 C3 D29 C4 D1 C4 D29 C5 D1 C5 D29 C6 D1 C6 D29 C7 D1 C7 D29 C8 D1 C8 D29 C9 D1 C9 D29
0 -5 -10 -15 -20 -25
Mean change from baseline
Worse
Ripretinib Sunitinib MCID
Ripretinib, n: 159 165 135 133 93 105 67 89 68 81 56 70 52 55 44 54 34
Sunitinib, n: 166 164 128 131 98 108 75 97 62 77 54 69 47 52 34 41 29

C.

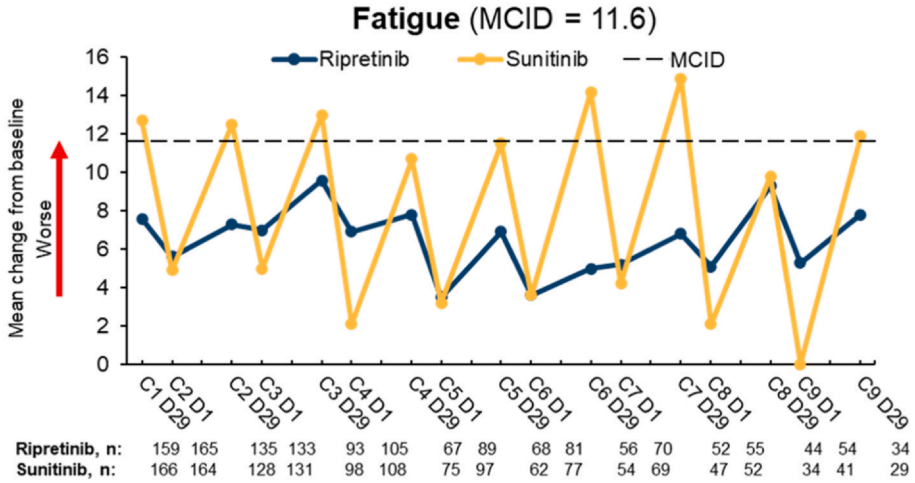

Fatigue (MCID = 11.6)
Ripretinib Sunitinib MCID
16 14 12 10 8 6 4 2 0
Mean change from baseline
Worse
C1 D29 C2 D1 C2 D29 C3 D1 C3 D29 C4 D1 C4 D29 C5 D1 C5 D29 C6 D1 C6 D29 C7 D1 C7 D29 C8 D1 C8 D29 C9 D1 C9 D29
Ripretinib, n: 159 165 135 133 93 105 67 89 68 81 56 70 52 55 44 54 34
Sunitinib, n: 166 164 128 131 98 108 75 97 62 77 54 69 47 52 34 41 29

Fig. 2. Change from baseline EORTC QLQ-C30 score over time in (A) role functioning, (B) physical functioning, and (C) fatigue. MCIDs were calculated as one half of the mean standard deviation of the two treatment arms at baseline based on all patients in the ITT population with evaluable baseline data and are marked with a dashed line for each scale; results for all scales at all PRO assessments from C1D29–C9D29 are presented in the supplement. Scores are reported out of 100, and for functioning scales, a higher score represents a higher level of functioning, corresponding to higher QoL. For symptom scales, a higher score represents higher levels of symptomatology, corresponding to lower QoL. C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer-30; ITT, intention-to-treat; MCID, minimum clinically important difference; PRO, patient-reported outcome; QoL, quality of life.

from baseline in QLQ-C30 functional scales on D1 assessments across cycles. However, on D29 assessments, patients receiving sunitinib generally experienced greater deterioration from baseline that exceeded the MCID in QLQ-C30 role functioning and physical functioning compared with ripretinib patients across cycles (Fig. 3A).

#### 3.2.2. *Symptom scales*

Patients receiving ripretinib generally reported better outcomes than patients receiving sunitinib across all QLQ-C30 symptom scales except constipation. At multiple assessments, patients receiving ripretinib reported significantly less increase in symptoms from baseline across multiple symptom scales compared with patients receiving sunitinib (Fig. 3B).

Patients receiving ripretinib and sunitinib generally experienced similar change from baseline in QLQ-C30 symptom scales on D1 assessments across cycles, but on D29 assessments, patients receiving sunitinib generally experienced greater increase in symptoms from baseline in QLQ-C30 fatigue, pain, appetite loss, nausea and vomiting, and diarrhoea compared with ripretinib patients across multiple cycles (Fig. 3B).

### 3.3. *TWiST analysis*

While the RMST for OS in the first year was similar between the two arms (340 days for ripretinib versus 338 days for sunitinib), patients receiving ripretinib spent more days in the TWiST state (alive, pre-progression, and without grade ≥3 TEAEs) relative to the RMST of OS in the first year (173/340 days, 50.9%) compared to patients receiving sunitinib (126/338 days, 37.3%), a difference of 13.6 percentage points (Table 2; Fig. 4). Patients receiving ripretinib also spent 50 fewer days in TOX than patients receiving sunitinib (103 versus 53 days). The time span was limited to 365 days because median follow-up was approximately 1 year at the time of the data cutoff. Sensitivity analyses with alternative time restrictions showed similar results.

After applying standardised utility weights to each health state, patients receiving ripretinib had 24 days more Q-TWiST than patients receiving sunitinib (Supplemental Table S1). These differences in TWiST and Q-TWiST were also observed in sensitivity analyses with TOX defined as days spent with grade ≥2 TEAEs (Supplemental Table S2, S3).

## 4. Discussion

In the INTRIGUE trial, there was no significant difference in PFS between ripretinib and sunitinib in adult patients with advanced GIST who progressed on, or were intolerant to, imatinib [24]. Ripretinib had a more favourable tolerability profile than sunitinib with more days of TWiST, greater Q-TWiST, and fewer days of toxicity. Patients receiving ripretinib reported significantly less decline in self-reported HRQoL. We found that patients receiving ripretinib experienced similar HRQoL to patients receiving sunitinib on D1 assessments. However, ripretinib patients experienced better HRQoL than patients receiving sunitinib at many D29 assessments, suggesting that ripretinib had a lesser impact on HRQoL compared with sunitinib following 4 weeks of treatment.

Constipation was the only item measured by the QLQ-C30 clearly less favourable for patients receiving ripretinib, with greater constipation reported among patients receiving ripretinib compared with patients receiving sunitinib at most PRO assessments. This result is consistent with the tolerability profile observed in the INTRIGUE trial [24]. Conversely, diarrhoea is commonly reported as a TEAE of sunitinib [14,32], and accordingly, patients receiving sunitinib reported substantially greater diarrhoea at a majority of assessments than patients receiving ripretinib.

Sunitinib treatment is commonly associated with a reduction in HRQoL [14]. To manage treatment toxicity, dose modifications are common in clinical practice. Sunitinib is often prescribed at a lower, continuous dose instead of the 4 weeks on/2 weeks off treatment regimen listed in the prescribing information [22,33]. For the purposes of the INTRIGUE study, sunitinib was administered per the prescribing information; however, about half of patients (111/221; 50.2%) had dose reductions, and 33/221 (14.9%) patients modified their sunitinib treatment regimen to continuous dosing at various levels [24]. Subgroup analyses were not performed due to the heterogeneity both in the timing of a

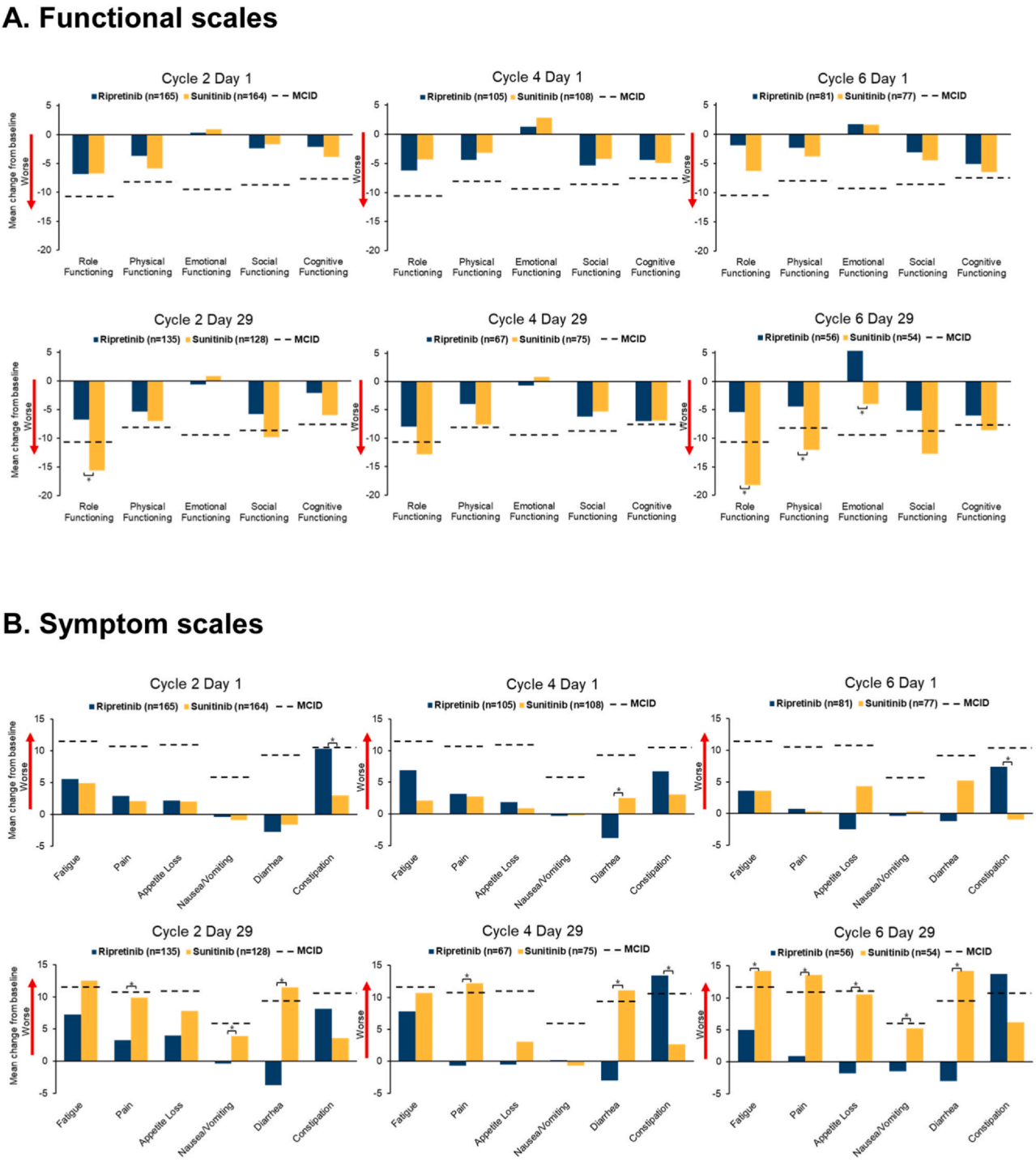



Fig. 3. Change from baseline EORTC QLQ-C30 score at day 1 versus day 29 for (A) functional scales and (B) symptom scales. MCIDs were calculated as one half of the mean standard deviation of the two treatment arms at baseline based on all patients in the ITT population with evaluable baseline data and are marked with a dashed line for each scale. The results for functional and symptom scales at all PRO assessments from C1D29–C9D29 are presented in the supplement; For functioning scales, scores are reported out of 100, and a higher score represents a higher level of functioning, corresponding to higher QoL. For symptom scales, a higher score represents higher levels of symptomatology, corresponding to lower QoL; *indicates $p < 0.05$ between the ripretinib and sunitinib groups; no multiple hypothesis testing adjustment applied. C, cycle; D, day; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Cancer-30; ITT, intention to treat; MCID, minimum clinically important difference; PRO, patient-reported outcomes; QoL, quality of life.

Table 2
TWiST analysis: restricted mean survival time by state in the first 365 days of follow-up, based on grade ≥3 TEAEs.

| State | Ripretinib | Sunitinib | Difference |
|---|---|---|---|
| Mean days alive (OS) | 340 | 338 | 2 |
| Mean days of relapse (REL state) | 114 | 109 | 5 (95% CI: −19, 30) |
| Mean days with grade ≥3 TEAEs (TOX state) | 53 | 103 | −50 (95% CI: −85, −9) |
| Mean days alive, pre-progression, without grade ≥3 TEAEs (TWiST state) | 173 | 126 | 47 (95% CI: 11, 76) |

CI, confidence interval; OS, overall survival; REL, relapse state; TEAE, treatment emergent adverse event; TOX, toxicity state; TWiST, time without symptoms and toxicity.

dosing regimen switch and in regimens among patients with a recorded switch, including post-switch dose increases and interruptions.

While a continuous lower dosing regimen may lessen treatment toxicity, it may also prolong treatment exposure. In an open-label treatment-use study, patients receiving altered dosing regimens of sunitinib remained on treatment longer but experienced similar rates of grade 3 and 4 TEAEs as patients receiving standard dosing, even after adjusting for treatment duration [34]. In the INTRIGUE trial, the daily dosing regimen was not modified for patients receiving ripretinib, but dose reductions were implemented in 44/223 patients (19.7%) [24]. Further research will be necessary to determine the relative HRQoL impact of ripretinib versus other TKIs.

The differences in dosing regimens between ripretinib and sunitinib were evident in the treatment impact on patient HRQoL. As expected with the 4 weeks on/2 weeks off dosing regimen for sunitinib [35], patients reported significant deterioration in HRQoL compared to baseline across multiple domains on D29 assessments after 4 weeks of continuous sunitinib treatment. D1 assessments, which occurred after 2 weeks without daily treatment, indicated a smaller decline from baseline HRQoL. For patients receiving ripretinib, patient-reported HRQoL was similar at D1 and D29 assessments. For all QLQ-C30 symptom scales except constipation, the patients receiving continuous ripretinib had similar HRQoL to sunitinib arm patients at D1 assessments, who had not received sunitinib for 2 weeks. Thus, patients receiving ripretinib are likely to experience stable, and, on average, better HRQoL throughout treatment.

The TWiST analysis is consistent with the PRO results, indicating that ripretinib has less toxicity and HRQoL impact compared with sunitinib. Despite similar OS and PFS for ripretinib and sunitinib, patients receiving ripretinib experienced a 13.6% gain in TWiST relative to the RMST of OS in the first year compared to patients receiving sunitinib. Thus, patients receiving ripretinib experienced more time with good HRQoL than patients receiving sunitinib while receiving similar survival benefit.

While no single measure can capture the entire patient experience, TWiST and PRO results considered in tandem can provide a more complete picture [36]. These analyses indicate that patients receiving ripretinib generally experienced better HRQoL than patients receiving sunitinib. Some TEAEs were more common in patients receiving ripretinib than sunitinib in the INTRIGUE trial, including alopecia, myalgia, abdominal pain, muscle spasms, and pruritus [24]. However, all grade ≥2 TEAEs are reflected in TWiST sensitivity analyses, which are consistent with the primary analyses in demonstrating greater TWiST for patients receiving ripretinib versus sunitinib.

There is an increasing recognition that the assessment of treatment options should incorporate not only the objective impact on response rate, PFS, and OS, but also the impact a treatment has on the patient experience [17,18,20]. This analysis provides a novel benchmark of a HRQoL assessment for patients with GIST in a second-line setting for both the standard-of-care, sunitinib, as well as ripretinib. These findings should be considered when making an overall assessment of ripretinib as a treatment option for advanced GIST.

Despite not meeting the primary endpoint of superior PFS compared with sunitinib in INTRIGUE, patients receiving ripretinib experienced better HRQoL than patients receiving sunitinib during the dosing period, and experienced similar HRQoL to patients who had not received sunitinib for 2 weeks for all QLQ-C30 domains expect constipation. The use of ripretinib may therefore provide meaningful clinical benefit from the patient perspective and a favourable safety profile to patients with advanced GIST previously treated with imatinib.

## Data sharing statement

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.

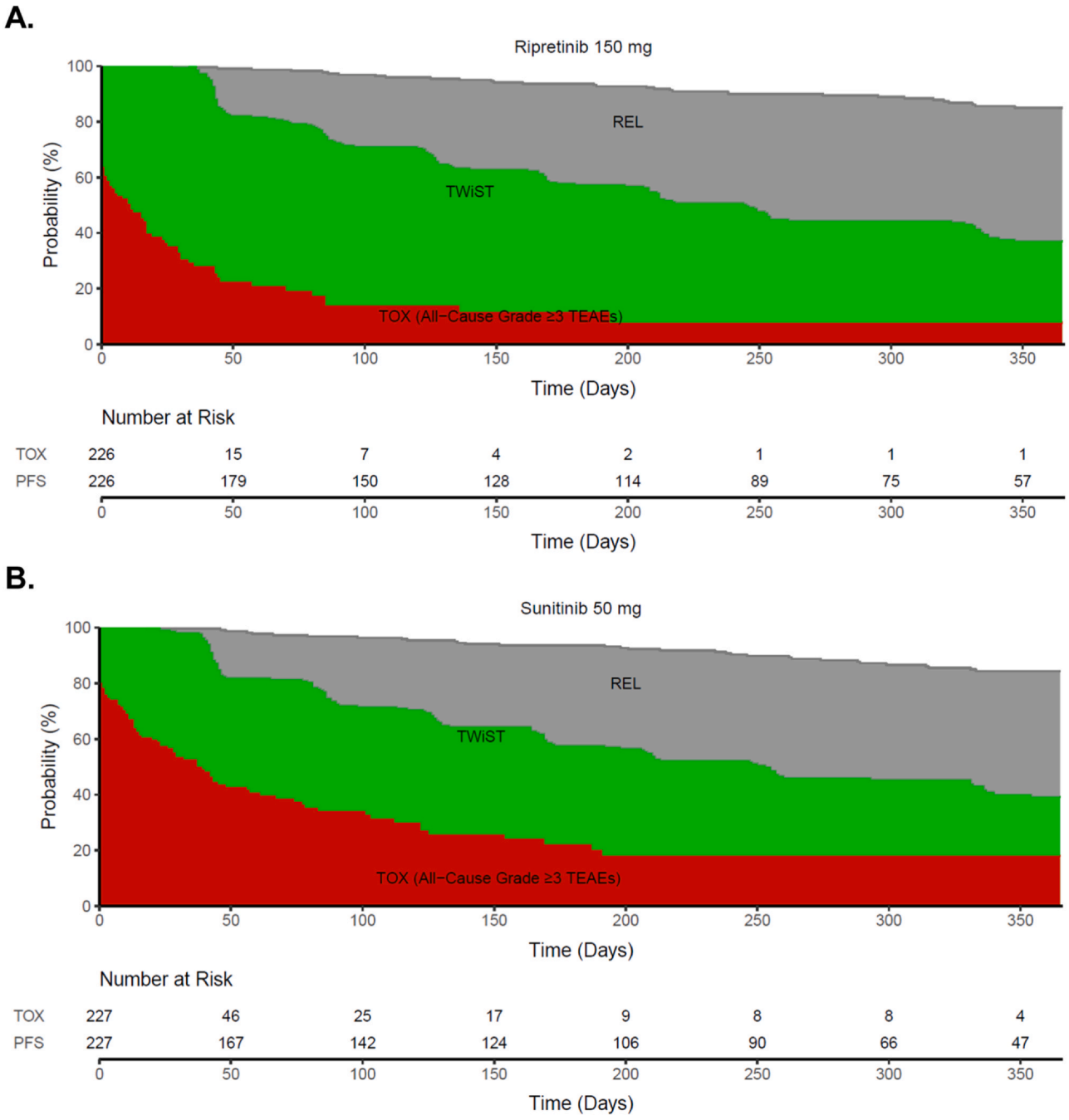



Fig. 4. Kaplan-Meier survival plots of REL, TWiST, and TOX states based on grade ≥3 all-cause TEAEs (ITT set). ITT, intention-to-treat; PFS, progression-free survival; REL, relapse state; TEAE, treatment-emergent adverse event; TOX, toxicity state; TWiST, time without symptoms and toxicity.

## Prior presentation

This study was presented in part at the ASCO Annual Meeting 2022, June 3–7, 2022, Chicago, IL.

## Author contributions

Substantial contributions to study conception and design: HG, RLJ, JYB, SG, MvM, JRZ, JT, SA, MLS, RRS, MCH, and SB. Provision of study material or patients: HG, RLJ, JYB, SG, MvM, JRZ, JT, YKK, SA, ALC, NS, MCH, and SB. Collection and assembly of data: All authors. Substantial contributions to analysis and interpretation of the data: All authors. Drafting the article or revising it critically for important intellectual content: All authors. Final approval of the version of the article to be published and accountability for all aspects of the work: All authors.

## Funding

This study was sponsored by Deciphera Pharmaceuticals, LLC. This article was based on the original study INTRIGUE (NCT03673501) sponsored by Deciphera Pharmaceuticals, LLC. Support for third-party writing assistance for this article, provided by Hannah L Fox, PhD, and Alex Emerson, BA, of Costello Medical, Boston, MA, USA, was funded by Deciphera Pharmaceuticals, LLC in accordance with Good Publication Practice (GPP) 2022 guidelines (https://www.ismpp.org/gpp-2022).

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Attia reports institutional research funding from AB Science, Adaptimmune, Advenchen Laboratories, Ayala Pharmaceuticals, Bavarian Nordic, Bayer, Blueprint Medicines, Boehringer Ingelheim, BTG, C4 Therapeutics, CBA Pharma, Deciphera Pharmaceuticals, Eli Lilly & Co, Epizyme, FORMA Therapeutics, Genmab, GlaxoSmithKline, Gradalis, Incyte, InhibRx, Karyopharm Therapeutics, Merck, Monopar Therapeutics, Novartis, Noxopharm, Philogen, PTC Therapeutics, Rain Therapeutics, Salarius Pharmaceuticals, Springworks, Takeda, Theseus Pharmaceuticals, TRACON Pharmaceuticals and Trillium Therapeutics; and personal research funding from the Desmoid Tumour Research Foundation. Dr. Bauer reports honoraria from Novartis; advisory board fees from Roche; consulting fees from Adcendo, Bayer, Blueprint Medicines, Boehringer Ingelheim, Cogent Biosciences, Daiichi Sankyo, Deciphera Pharmaceuticals, Eli Lilly & Co, Exelixis, GlaxoSmithKline, Incyte, Nanobiotix, Novartis and PharmaMar; institutional research funding from Novartis; and travel support from PharmaMar. Dr. Becker has no financial interests to disclose. Dr. Blay reports leadership at Innate Pharma; honoraria from AstraZeneca, Bayer, Bristol Myers Squibb, Deciphera Pharmaceuticals, Ignyta, Merck, PharmaMar and Roche; consulting fees from Bayer, Blueprint Medicines, Deciphera Pharmaceuticals, Karyopharm Therapeutics, PharmaMar and Roche; institutional research funding from AstraZeneca, Bristol Myers Squibb, Bayer, Deciphera Pharmaceuticals, GlaxoSmithKline, Merck, Novartis, OSE Pharma, PharmaMar and Roche; and travel support from Roche. Dr. Boye reports honoraria from Eli Lilly & Co and Novartis; consulting fees from Bayer and GlaxoSmithKline; and institutional research funding from Eli Lillly & Co and Merck. Dr. Chi reports consulting fees from Deciphera Pharmaceuticals, Exelixis, NewBay, Novartis and Zai Lab; institutional research funding from Deciphera Pharmaceuticals and Pfizer/Array; and is a shareholder of Oric Pharma.Dr. Druta reports consulting fees from Eisai and Eli Lilly & Co; and speaker's bureau fees from Eisai and Eli Lilly & Co. Dr. Gelderblom reports institutional research funding from Daiichi Sankyo, Deciphera Pharmaceuticals, Ipsen and Novartis. Dr. George reports consulting fees from Bayer, Blueprint Medicines, Daiichi Sankyo, Deciphera Pharmaceuticals, Eli Lilly & Co, Kayothera, Immunicum, MORE Health, Research to Practice and UpToDate; institutional research funding from BioAtla, Blueprint Medicines, Daiichi Sankyo, Deciphera, Eisai, IDRX, Merck, Springworks, Theseus Pharmaceuticals and TRACON Pharma; honoraria from CStone Pharmaceuticals; patents, royalties, or other intellectual property with UpToDate; other financial relationships with Research to Practice and WCG/Ayala; and is a shareholder of Abbott Laboratories. Dr. Goldstein reports consulting fees from Deciphera Pharmaceuticals. Dr. Harrow is an employee and shareholder of Deciphera Pharmaceuticals. Dr. Heinrich reports honoraria from Novartis; consulting fees from Blueprint Medicines, Deciphera Pharmaceuticals, Novartis and Theseus Pharmaceuticals; and a patent on the treatment of GIST licensed to Novartis. Dr. Jones reports consulting fees from Adaptimmune, Astex, Athenex, Bayer, Boehringer Ingelheim, Blueprint Medicines, Clinigen, Eisai, Eli Lilly & Co, Epizyme, Daiichi Sankyo, Deciphera Pharmaceuticals, Immunedesign, Immunicum, Karma Oncology, Merck, Mundipharma, PharmaMar, Springworks, SynOx, TRACON Pharmaceuticals and UpToDate. Dr. Kang reports consulting fees from ALX Oncology, Amgen, Novartis, Blueprint Medicines, Bristol Myers Squibb, Daehwa, Macrogenics, Surface Oncology and Zymeworks. Dr. Le Cesne reports honoraria from Bayer, Deciphera Pharmaceuticals, and PharmaMar. Dr. Razak reports consulting fees from Adaptimmune, Bayer, GlaxoSmithKline, Medison, Inhibrx; and research funding from AbbVie, Adaptimmune, Amgen, Blueprint Medicines, Bristol Myers Squibb, Daiichi Sankyo, Deciphera Pharmaceuticals, GlaxoSmithKline, Iterion Therapeutics, Karyopharm Therapeutics, Merck, MedImmune, Neoleukin Therapeutics, Pfizer, Roche/Genentech, Rain Therapeutics and Symphogen; and served as expert testimony for Medison. Dr. Reichmann is an employee and shareholder of Deciphera Pharmaceuticals. Dr. Ruiz-Soto is an employee of Deciphera Pharmaceuticals; a shareholder of Deciphera Pharmaceuticals and Immunogen; and is an inventor in three patents with Immunogen and pending patents at Deciphera Pharmaceuticals, the rights for which have been transferred to Immunogen and Deciphera, respectively; Dr. Ruiz-Soto has not received and will not receive royalties from these patents. Dr. Rutkowski reports honoraria from AstraZeneca, Bristol Myers Squibb, Merck, Novartis, Pierre Fabre, and Sanofi. Dr. Sanchez reports honoraria from AstraZeneca, Novartis, Pfizer and Roche;

and research funding from Pfizer, Novartis and Roche. Dr. Serrano reports honoraria from Bayer and Blueprint Medicines; institutional research funding from Bayer, Deciphera Pharmaceuticals, Karyopharm Therapeutics and Pfizer; consulting fees from Blueprint Medicines, Cogent Biosciences, Deciphera Pharmaceuticals and Immunicum; and travel support from Bayer, Eli Lilly & Co, Novartis, Pfizer and PharmaMar. Dr. Siontis reports consulting fees from Deciphera Pharmaceuticals and institutional research funding from Advenchen and Deciphera Pharmaceuticals. Dr. Sherman reports employment, leadership, and stock or other ownership interests of Deciphera Pharmaceuticals and Pieris Pharmaceuticals. Dr. Somaiah reports consulting fees from Aadi Biosciences, Boehringer Ingelheim and Epizyme and research funding from Advenchen, Ascentage, AstraZeneca, Cogent, Deciphera Pharmaceuticals, GlaxoSmithKline, and Innovent. Dr. Steeghs reports consulting fees from Boehringer Ingelheim, Cogent Biosciences, Ellipses Pharma and Luszana; institutional research funding from AbbVie, Actuate Therapeutics, Amgen, Array, Ascendis Pharma, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Cantargia, CellCentric, Cogent, Cresecendo Biologics, Cytovation, Deciphera Pharmaceuticals, Eli Lilly & Co, Exelixis, Genentech, GlaxoSmithKline, Incyte, InteRNA, Janssen, Kinnate Biopharma, Luszana, Merck, Merus, Molecular Partners, Navire Pharma, Novartis, Numab Therapeutics, Pfizer, Relay Pharmaceuticals, Revolution Medicine, Roche, Sanofi, Seattle Genetics, Taiho and Takeda. Dr. Trent reports consulting fees from Adcendo, AADI Bioscience, Cogent, Deciphera Pharmaceuticals, Daiichi Sankyo and Foghorn Therapeutics. Dr. von Mehren reports consulting fees from Deciphera Pharmaceuticals, GlaxoSmithKline and Moleculin; institutional research funding from ASCO, Ayala, Deciphera Pharmaceuticals, Genmab, Gradalis, Novartis, Solaris Health, Sumitomo Pharma Oncology and Theseus Pharmaceuticals; and another financial relationship with NCCN. Dr. Zalcberg reports leadership at ICON Group, Lipotek and Praxis; honoraria from Deciphera Pharmaceuticals, Halozyme, Gilead Sciences, Merck Serono, Specialised Therapeutics and Targovax; consulting fees from 1Globe Health Institute, Centre for Emerging and Neglected Diseases (CEND), Deciphera Pharmaceuticals, FivePHusion, Genor BioPharma, Halozyme, Lipotek, Merck, Merck Serono, Novotech, Revolution Medicine, Specialised Therapeutics and Targovax; institutional research funding from AstraZeneca, Bristol Myers Squibb, Eisai, Ipsen, IQVIA, Medtronic, Merck Serono, Mylan and Pfizer; stock or other ownership of Amarin Corporation, Biomarin, Concert Pharmaceuticals, Frequency Therapeutics, Gilead Sciences, Madrigal Pharmaceuticals, Moderna Therapeutics, Novavax, Opthea, Orphazyme, Twist Bioscience, UniQure and Zogenix; and travel support from AstraZeneca, Deciphera Pharmaceuticals, Merck, Merck Serono and Sanofi.

## Acknowledgements

The INTRIGUE study was funded by Deciphera Pharmaceuticals, LLC. The authors thank the patients, the investigators and their teams who took part in this study. The authors also acknowledge Leanne Wilson, PhD, and Trang Pham, MPH, of Deciphera Pharmaceuticals, LLC, Waltham, MA, USA, for publication coordination and statistical support, respectively, and Hannah L Fox, PhD, and Alex Emerson, BA, of Costello Medical, Boston, MA, USA, for medical writing and editorial assistance based on the authors' input and direction. 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).

## Appendix A. Supporting material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113245.

## References

[1] Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. The Lancet 2007;369:1731–41.
[2] Soreide K, Sandvik OM, Soreide JA, et al. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. Cancer Epidemiol 2016;40:39–46.
[3] Vallilas C, Sarantis P, Kyriazoglou A, et al. Gastrointestinal stromal tumours (GISTs): novel therapeutic strategies with immunotherapy and small molecules. Int J Mol Sci 2021;22:493.
[4] Kelly CM, Gutierrez Sainz L, Chi P. The management of metastatic GIST: current standard and investigational therapeutics. J Hematol Oncol 2021;14:2.
[5] Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumours. Science 2003;299:708–10.
[6] Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumours expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008;26:626–32.
[7] Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. The Lancet 2006;368:1329–38.
[8] Pfizer Labs: Sutent (Sunitinib Malate) capsules for oral use. Prescribing information, 2021.
[9] Chamberlain F, Farag S, Williams-Sharkey C, et al. Toxicity management of regorafenib in patients with gastro-intestinal stromal tumour (GIST) in a tertiary cancer centre. Clin Sarcoma Res 2020;10:1.
[10] Blay J-Y, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:923–34.
[11] Deciphera Pharmaceuticals LLC: QINLOCK (Ripretinib) tablets: US prescribing information, 2021.

[12] Smith BD, Kaufman MD, Lu WP, et al. Ripretinib (DCC-2618) is a switch control kinase inhibitor of a broad spectrum of oncogenic and drug-resistant KIT and PDGFRA variants. Cancer Cell 2019;35(738–751):e9.
[13] Casali PG, Zalcberg J, Le Cesne A, et al. Ten-year progression-free and overall survival in patients with unresectable or metastatic GI stromal tumours: long-term analysis of the European organisation for research and treatment of cancer, Italian sarcoma group, and Australasian gastrointestinal trials group intergroup phase III randomized trial on imatinib at two dose levels. J Clin Oncol 2017;35:1713–20.
[14] van de Wal D, Elie M, Le Cesne A, et al. Health-related quality of life and side effects in gastrointestinal stromal tumour (GIST) patients treated with tyrosine kinase inhibitors: a systematic review of the literature. Cancers (Basel) 2022;14:1832.
[15] Eichler M, Pink D, Menge F, et al. Quality of life of GIST patients with and without current tyrosine kinase inhibitor treatment: cross-sectional results of a German multicentre observational study (PROSa). Eur J Cancer Care (Engl) 2021;30:e13484.
[16] Gupta A, Eisenhauer EA, Booth CM. The time toxicity of cancer treatment. J Clin Oncol 2022;40:1611–5.
[17] Fauske L, Hompland I, Lorem G, et al. Perspectives on treatment side effects in patients with metastatic gastrointestinal stromal tumour: a qualitative study. Clin Sarcoma Res 2019;9:6.
[18] Schnipper LE, Davidson NE, Wollins DS, et al. American Society of Clinical Oncology statement: a conceptual framework to assess the value of cancer treatment options. J Clin Oncol 2015;33:2563–77.
[19] Gnanasakthy A. FDA guidance on assessment of patient-reported outcomes in cancer trials: a breath of fresh air or a storm in a teacup? Patient 2021;14:695–7.
[20] Cherny NI, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefit scale version 1.1. Ann Oncol 2017;28:2340–66.
[21] Schvartsman G, Wagner MJ, Amini B, et al. Treatment patterns, efficacy and toxicity of regorafenib in gastrointestinal stromal tumour patients. Sci Rep 2017;7:9519.
[22] George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. Eur J Cancer 2009;45:1959–68.
[23] Schoffski P, George S, Heinrich MC, et al. Patient-reported outcomes in individuals with advanced gastrointestinal stromal tumour treated with ripretinib in the fourth-line setting: analysis from the phase 3 INVICTUS trial. BMC Cancer 2022;22:1302.
[24] Bauer S, Jones RL, Blay JY, et al. Ripretinib versus sunitinib in patients with advanced gastrointestinal stromal tumour after treatment with imatinib (INTRIGUE): a randomized, open-label, phase III trial. J Clin Oncol 2022;40:3918–28.
[25] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastrointestinal Stromal Tumors Version 1.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed March 17, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. NCCN=National Comprehensive Cancer Network® (NCCN®).
[26] Fayers P, Bottomley A. Quality of life research within the EORTC—the EORTC QLQ-C30. Eur J Cancer 2002;38:125–33.
[27] Gelber RD, Gelman RS, Goldhirsch A. A quality-of-Life-oriented endpoint for comparing therapies. Biometrics 1989;45:781–95.
[28] Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.
[29] Fayers P, Aaronson NK, Bjordal K, et al. The EORTC QLQ-C30 scoring manual (3rd edition). Brussels, European organisation for research and treatment of cancer, 2001.
[30] Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. Med Care 2003;41:582–92.
[31] Gelber RD, Cole BF, Gelber S, et al. Comparing treatments using quality-adjusted survival: the Q-TWiST method. Am Stat 1995;49:161–9.
[32] Sehdev S. Sunitinib toxicity management—a practical approach. Can Urol Assoc J 2016;10:S248–51.
[33] Schwartz GK. Ripretinib and the failure to advance GI stromal tumour therapy in the age of precision medicine. J Clin Oncol 2022;40:3903–6.
[34] Reichardt P, Kang YK, Rutkowski P, et al. Clinical outcomes of patients with advanced gastrointestinal stromal tumours: safety and efficacy in a worldwide treatment-use trial of sunitinib. Cancer 2015;121:1405–13.
[35] Motzer RJ, Hutson TE, Olsen MR, et al. Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. J Clin Oncol 2012;30:1371–7.
[36] Husson O, Jones RL. Q-TWiST: what really matters to the cancer patient? Cancer 2017;123:2200–2.