Abstract
Ripretinib (Qinlock®) is a small molecule inhibitor of the receptor tyrosine kinases KIT and platelet-derived growth factor receptor α (PDGFRA) and is approved for the treatment of gastrointestinal stromal tumours as a fourth-line of therapy. After successive cycles of treatment, gastrointestinal stromal tumours can carry a wide array of mutations, which makes resistance to treatment more likely. Ripretinib has a dual mechanism of action that allows it to target a broad spectrum of mutations in KIT or PDGFRA. The pivotal phase III INVICTUS trial demonstrated an increase of progression-free survival in patients receiving ripretinib compared with placebo, with efficacy being maintained across patients with KIT exon 9, 11, 13 and 17 mutations. Ripretinib has acceptable tolerability, with the most common drug-related grade 3 or 4 adverse events being lipase increases, hypertension, fatigue and hypophosphataemia. Ripretinib is therefore a valuable additional line of therapy available for the management of gastrointestinal stromal tumours.

Plain Language Summary
The receptor tyrosine kinases KIT and platelet-derived growth factor receptor α (PDGFRA) regulate cell growth and survival; mutations in the genes of these proteins are the most common causes of gastrointestinal stromal tumours. Drugs that target kinases are a mainstay in the treatment of these cancers; however, new mutations often occur that make tumours resistant to kinase inhibitors. Ripretinib (Qinlock®) is approved for patients with gastrointestinal stromal tumours after the tumour has become resistant to three or more other kinase inhibitors. In a pivotal phase III clinical trial in patients with gastrointestinal stromal tumours and who had failure with three or more prior treatments, ripretinib significantly delayed disease progression compared with placebo. Ripretinib has an acceptable side effect profile, with the most common drug-related side effects being alopecia, muscle pain and nausea. Thus, ripretinib is a valuable treatment option in the management of advanced gastrointestinal stromal tumours.
1 Introduction

Gastrointestinal stromal tumours are soft tissue sarcomas that can occur anywhere in the gastrointestinal tract [1]. They have an estimated annual incidence of 6–22 per million worldwide [1]. The molecular drivers of these malignancies are fairly well understood, with the majority of cases being driven by mutations in the genes that encode the receptor tyrosine kinase proteins KIT (69–83%) and platelet-derived growth factor receptor α (PDGFRα) (5–15%) [1–3].

Mutation of receptor tyrosine kinase proteins often leads to unregulated initiation of phosphorylation cascades, which promotes cellular proliferation and survival [1]. In KIT, mutations in the juxtamembrane domain (exon 11) or membrane proximal extracellular region (exon 9) lead to signalling molecule-independent activation; these mutations account for around 60% and 9–10% of all gastrointestinal stromal tumours, respectively [1, 3]. In contrast, mutations in PDGFRα are frequently in the activation loop (exon 18) [4], which interacts with the juxtamembrane domain to regulate the activity state of the protein [1]. The D842V mutation in exon 18 of PDGFRα account for 9–10% of all gastrointestinal stromal tumours [1].

Imatinib was the first kinase inhibitor used to treat advanced gastrointestinal stromal tumours [1]. It works by binding to the kinase adenosine triphosphate (ATP)-binding pocket of kinase proteins and locking the protein in an inactive state [5]. While imatinib is an effective treatment for advanced gastrointestinal stromal tumours, tumours often develop secondary mutations and become resistant to treatment [6]. Secondary mutations frequently occur in the ATP-binding pocket (e.g. KIT exons 13 and 14) or in the activation loop (e.g. KIT exons 17 and 18) [1]. Newer generations of kinase inhibitors, such as sunitinib and regorafenib, are able to target some, but not all, of these mutants [2]. One of the main issues is inter-tumour heterogeneity, whereby over time different clones of the primary tumour develop separate resistance mechanisms resulting in a subset of malignancies within a patient escaping treatment [1]. Therefore, a drug that is capable of inhibiting a broad spectrum of receptor tyrosine kinase mutants represented an unmet clinical need.

Ripretinib (Qinlock®) is a kinase inhibitor indicated in the USA [7] and the EU [8] for the treatment of adult patients with advanced gastrointestinal stromal tumour who have received prior treatment with three or more kinase inhibitors, including imatinib. Ripretinib has shown activity against a wide range of KIT and PDGFRα mutants [9]. This article reviews the efficacy and tolerability of ripretinib as fourth- or later-line treatment of gastrointestinal stromal tumours, with a brief overview of its pharmacological properties.

2 Pharmacodynamic Properties of Ripretinib

Ripretinib and its equally potent active metabolite, DP-5439, are small molecule switch control tyrosine kinase inhibitors which potently inhibit a range of kinases including KIT and PDGFRα, as well as many of their clinically relevant activating mutants [9]. Other kinases inhibited by ripretinib include B-Raf, vascular endothelial growth factor receptor-2 (VEGFR2), platelet-derived growth factor receptor β (PDGFRβ) and TEK receptor tyrosine kinase (TIE2); these off-target interactions may have implications for potential adverse events (Sect. 5.1). Co-crystallography studies of inhibitors with KIT have shown that ripretinib analogues act through binding to the juxtamembrane domain switch pocket of activated tyrosine kinase and displacing the activation loop; this promotes switching of the kinase back to an inactive state. It then forms further interactions with the activation loop and locks the protein in the inactive state [9].

Based on in vitro studies, ripretinib inhibits wild-type KIT and PDGFRα as well as a broad range of KIT and PDGFRα mutants [9]. Notably, in these experiments, ripretinib was able to inhibit KIT and PDGFRα activity in clinically relevant mutant variants that were resistant to other kinase inhibitors. For example, ripretinib inhibited recombinant KIT carrying V654A (exon 13), T670I (exon 14), D816H/V (exon 17) mutations with concentrations required for 50% inhibition (IC50) of 9.2–25 nM, whereas IC50 values were all > 3300 nM for these mutants with imatinib and were ≥ 1450 nM for D816H/V mutants with sunitinib and regorafenib. Similarly, ripretinib had an IC50 value for recombinant PDGFRα D842V of 36 nM compared with values of 270 nM for imatinib and 550 nM for sunitinib. The ability of ripretinib to inhibit kinase activity in tumours that are resistant to other kinase inhibitors is further supported by studies in cell lines and animal models [9].

Ripretinib also arrests proliferation of KIT and PDGFRα mutant gastrointestinal stromal tumour cell lines. Furthermore, ripretinib has been shown to prevent the emergence of secondary KIT mutants in saturation mutagenesis assays. Ripretinib anti-tumour activity has also been demonstrated in vivo in gastrointestinal stromal tumour and lung cancer xenograft mouse models [9].

3 Pharmacokinetic Properties of Ripretinib

The pharmacokinetics of ripretinib and DP-5439 have been evaluated in patients with advanced malignancies [7, 8, 10]. In a phase I trial (NCT02571036) after a single oral dose of
ripretinib 150 mg in patients with advanced malignancies, mean peak plasma concentrations (C_{max}) of ripretinib and DP-5439 were reached in 4.0 h and 15.6 h, respectively [10]. The area under the concentration-time curve from 0 to 24 h (AUC_{24}) increased roughly dose proportionally over a dose range of 20–250 mg for ripretinib but the C_{max} was less than dose proportional, while both C_{max} and AUC_{24} increased less than dose proportionally for DP-5439 over the same dose range [10].

The binding of ripretinib and DP-5439 to plasma proteins is ≥ 99% [7, 8]. Ripretinib and DP-5439 are extensively distributed to peripheral tissues, with mean apparent volumes of distribution of 302–307 L and 491–507 L, respectively. The drug and its active metabolite reached steady state concentrations after 14 days [7, 8], with an accumulation ratio for AUC_{12} of 1.7 and 5.29, respectively [7]. In patients with advanced malignancies, at day 15 of once-daily doses of ripretinib 150 mg, mean trough plasma concentrations (C_{trough}) for ripretinib and DP-5439, respectively, were 284 ng/mL and 546 ng/mL, while AUC_{12} values were 5678 ng·h/mL and 7138 ng·h/mL [10].

In vitro, both ripretinib and DP-5439 were metabolised by CYP3A4/5, CYP2D6 and CYP2C8 enzymes [11]. The mean apparent oral clearance of ripretinib and DP-5439, respectively, is approximately 15 L/h and 18 L/h and their mean half-lives are 13–15 h and 16–18 h [7, 8]. A negligible (< 1%) amount of the ripretinib dose is excreted in the urine as ripretinib or DP-5439, while 34% and 6% of the oral dose is eliminated as ripretinib and DP-5439 in the faeces [7, 8].

In healthy adult subjects concurrent usage of a strong CYP3A inhibitor (itraconazole) or inducer (rifampicin) with a single dose of ripretinib resulted in clinically relevant increases and reductions, respectively, in ripretinib exposure [11]. As ripretinib and its active metabolite are metabolised by CYP3A4/5, coadministration with strong or moderate CYP3A inducers should be avoided. If coadministration of ripretinib with moderate [7, 8] or strong [8] CYP3A inducers cannot be avoided, an increase in the ripretinib dosing frequency may be required. Patients receiving known CYP3-family inhibitors should be closely monitored for adverse events. Ripretinib and DP-5439 are also substrates of P-glycoprotein [8]. Inhibitors of P-glycoprotein could hinder the clearance of the drug and its active metabolite from the body; caution is advised when using ripretinib with strong P-glycoprotein inhibitors [7, 8].

### 4 Therapeutic Efficacy of Ripretinib

An open-label phase I trial (NCT02571036) in adult (age ≥ 18 years) patients with advanced gastrointestinal stromal tumours (with progression or intolerance to ≥ 1 line of prior systemic therapy) or other advanced malignancies established the recommended dose of ripretinib as 150 mg once daily based on pharmacological and tolerability data [10]. In this study, the maximum tolerated dose was not reached at the highest dose (200 mg twice daily) but ripretinib exposure with 150 mg once daily was above the predicted threshold (based on preclinical models) required for efficacy in > 90% of patients. In addition, the phase I trial provided early evidence for the efficacy of ripretinib in the treatment of refractory advanced gastrointestinal stromal tumours [10]. This section will focus on the subsequent INVICTUS trial [12], which was the basis for the approval of ripretinib in the USA and EU.

INVICTUS was a multicentre, randomised, double-blinded, placebo-controlled phase III trial [12]. Patients were eligible for the study if they had gastrointestinal stromal tumours and had progressed while on, or were intolerant to, imatinib, sunitinib and regorafenib. Patients with all types of gastrointestinal stromal tumours were included in the study, including those with no KIT and PDGFRα mutations. Patients had a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale, had adequate organ function and bone marrow reserves. Patients were excluded if they had left ventricular function < 50% [13] or if they received anticancer therapy 14 days or five times the half-life of the therapy drug prior to the first dose of study drug, whichever was longer [12].

The clinical trial design is summarised in Fig. 1. Participants were randomised to ripretinib 150 mg or placebo once daily with stratification by both the number of therapies they had previously received (three vs four or more) as well as their ECOG performance status (0 vs 1 or 2) (Table 1, Fig. 1) [12]. Treatment was given in 28-day cycles, with patients assessed for tumour progression every cycle for the first four cycles and every two cycles thereafter. Disease progression was determined by blinded independent central review as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria [14], modified for gastrointestinal stromal tumours [15]. Dosage interruption and/or reduction at the discretion of the investigator was permitted to manage adverse events. Upon disease progression, patients from both groups were given the option to continue into the open-label phase of the trial [12]. In the open-label phase, patients in the ripretinib group could escalate the dose to ripretinib 150 mg twice daily or, if showing clinical benefit, continue ripretinib 150 mg once daily; patients in the placebo group could cross over to ripretinib 150 mg once daily, with the option of dose escalation to ripretinib 150 mg twice daily upon further disease progression [12].

The primary endpoint was progression-free survival and the key secondary endpoint was objective response rate; endpoints were assessed hierarchically [12]. At the time of primary analysis (May 31, 2019), the median duration of...
follow-up for patients in the ripretinib and placebo groups in the double-blinded phase was 6.3 months and 1.6 months, respectively [12].

Baseline characteristics were generally well balanced across groups, although patients randomised to ripretinib were slightly younger (median age 59 vs 65 years in the placebo group) and had slightly better performance status (44 vs 39% with ECOG performance status 0) [12]. In the ripretinib and placebo groups, respectively, 64% and 61% had received three prior therapies and 36% and 39% had received four or more prior therapies. In the ripretinib and placebo groups, respectively, the primary mutation was in KIT exon 11 in 55% and 64% of patients, in KIT exon 9 in 17% and 14%, other KIT in 2% and 5%, and in PDGFRA in 4% and 0%; 8% and 7% had wild-type KIT and PDGFRA, and 14% and 11% did not have mutation data available [12].

Ripretinib as fourth- or later-line therapy significantly improved progression-free survival in patients with advanced gastrointestinal stromal tumours (Table 1). Compared with placebo, ripretinib reduced the risk of progression or death by 85% (hazard ratio 0.15, 95% CI 0.09–0.25; \( p < 0.0001 \)). Kaplan–Meier-estimated 6-month progression-free survival rates were 51% (95% CI 39.4–61.4) for ripretinib recipients and 3.2% (95% CI 0.2–13.8) for placebo recipients [12]. The benefits of ripretinib were consistent in patient subgroups across a broad range of KIT mutation profiles, based on an exploratory analysis [13]. In the analysis, improved Kaplan–Meier progression-free survival in favour of ripretinib over placebo (hazard ratio 0.13–0.16) was seen in patients with exon 11, 9, 13 and 17 KIT mutations as detected in baseline tissue and/or liquid biopsies (patients were included in multiple groups if they had mutations in > 1 exon) [13].

Eight patients in the ripretinib group and no patients in the placebo group had a confirmed objective response (first key secondary endpoint), although the between-group difference did not reach statistical significance (\( p = 0.0504 \)) (Table 1) [12]. All responses were partial responses. In addition, 47% of ripretinib recipients versus 5% of placebo recipients had stable disease at 12 weeks. At data cut-off, one of the eight responders had progressed and the median duration of response had not been reached [12].

Although not formally assessed for statistical significance due to the hierarchical design of the study and the lack of statistical significance for the objective response rate, median overall survival was 15.1 months in patients randomised to ripretinib and 6.6 months in patients randomised to placebo (Table 1) [12]. The overall survival analysis included both the double-blind phase and the open-label phase of the trial, where 66% of placebo recipients crossed over to ripretinib. With longer-term follow up (for 19 months beyond the primary analysis), the median overall survival was 18.2 months in patients randomised to ripretinib and 6.3 months in patients randomised to placebo [16].

Fourteen months after initial data cut-off, 65 of the 85 patients randomised to ripretinib had developed progressive disease and of these, 43 patients had received a dose escalation of ripretinib to 150 mg twice daily [17].
who received ripretinib 150 mg twice daily, the median second progression-free survival period (measured from start of dose escalation to disease progression or death) was 3.7 months [17].

### 5 Tolerability of Ripretinib

Ripretinib 150 mg once daily had acceptable tolerability in patients with gastrointestinal stromal tumours across clinical trials [10, 12, 18]. In INVICTUS, tolerability was assessed in the double-blinded phase in patients who received at least one dose of study drug (ripretinib n = 85, placebo n = 43) [12]. Patients receiving ripretinib compared with placebo were treated for longer in the double-blinded phase, with a median follow-up period of 6.3 and 1.6 months, respectively (Sect. 4). Treatment-emergent adverse events were generally manageable with dose reduction or interruption [12].

The most common (incidence ≥ 20%) treatment-related adverse events with ripretinib were alopecia (49 vs 2% with placebo), myalgia (28 vs 9%), nausea (26 vs 2%), fatigue (26 vs 16%), palmar–plantar erythrodysesthesia syndrome (21 vs 0%) and diarrhoea (21 vs 7%) [12]. The most common (incidence ≥ 2%) study drug-related treatment-emergent adverse events of grade 3 or 4 with ripretinib were lipase increase (5 vs 0% with placebo), hypertension (4 vs 0%), hypophosphataemia (2 vs 0%) and fatigue (2 vs 2%). Treatment-related serious adverse events were experienced in eight (9%) patients in the ripretinib and three (7%) patients in the placebo group [12].

A numerically higher proportion of ripretinib than placebo recipients experienced treatment-emergent serious adverse events leading to dose reduction (6 vs 2%), treatment interruption (14 vs 7%) and treatment discontinuation (5 vs 2%) [12]. Of the four patients in the ripretinib group who discontinued treatment, the reason for discontinuation was cardiac failure, death of unknown cause, general physical health deterioration and palmar–plantar erythrodysesthesia. Deaths occurred in 14% and 30% of patients in the ripretinib and placebo groups, respectively; deaths were mainly due to disease progression. Of the deaths considered possibly treatment-related, one occurred in the ripretinib group (unknown cause) and one occurred in the placebo group (septic shock and pulmonary oedema) [12]. No new safety concerns for ripretinib were raised with longer-term follow-up (19 months beyond the primary analysis) [16].

Dose escalation of ripretinib to 150 mg twice daily had acceptable tolerability, with the most frequent (≥ 5%) new or worsening grade 3 or 4 treatment-emergent adverse events being anaemia [in 6 of 43 (14%) dose-escalated patients] and abdominal pain [3 of 43 (7%) dose-escalated patients] [17]. With treatment at this dosage, 19% of dose-escalated patients required a dose reduction, 26% a dose interruption and 7% had a treatment-emergent adverse event leading to discontinuation of ripretinib [17].

Based on the multinational, randomised, open-label, phase III INTRIGUE trial, it appears that ripretinib may have improved tolerability compared with sunitinib [18]. In INTRIGUE, patients with advanced gastrointestinal stromal tumours who had progressed on or had intolerance to imatinib were randomised 1:1 to ripretinib 150 mg once daily (continuous) or sunitinib 50 mg once daily (cycles of 4 weeks on, 2 weeks off). Whilst similar proportions of ripretinib recipients (n = 223; median treatment duration, 7.9 months) and sunitinib recipients (n = 221; median treatment duration, 6.5 months) experienced treatment-emergent serious adverse events (25.6 vs 25.8%), numerically fewer ripretinib than sunitinib recipients had treatment-emergent adverse events leading to dose reduction (20.2 vs 48.0%), dose interruption (29.1 vs 41.6%) or study drug discontinuation (3.6 vs 7.7%). Furthermore, the incidence of grade 3 or 4 treatment-emergent adverse events was lower among ripretinib recipients compared with sunitinib recipients (41.3 vs 65.6%; nominal p < 0.0001) as was the incidence of

### Table 1 Efficacy of ripretinib as fourth or later-line treatment for patients with gastrointestinal stromal tumours

| Endpoint                                      | Ripretinib (n = 85) | Placebo (n = 44) |
|-----------------------------------------------|---------------------|-----------------|
| Median progression-free survival [months (95% CI)] | 6.3 (4.6–6.9)       | 1.0 (0.9–1.7)   |
| Hazard ratio (95% CI)                         | 0.15 (0.09–0.25)*   |                 |
| Objective response rate [% (95% CI)]         | 9.4 (4.2–17.7)      | 0 (0–8)         |
| Median overall survival [months (95% CI)]    | 15.1 (12.3–15.1)    | 6.6 (4.1–11.6)  |
| Hazard Ratio (95% CI)                        | 0.36 (0.21–0.62)    |                 |

Data from the phase III INVICTUS trial [12]

*p < 0.0001 vs placebo

Endpoints are listed in the pre-specified order of hierarchical testing

Intention to treat population; presented data are based on analyses using the Kaplan-Meier method

Primary endpoint

No statistical analysis was performed because of hierarchical study design and the lack of statistical significance for the objective response rate
grade 3 or 4 drug-related treatment emergent adverse events (26.5% vs 55.2%) [18].

5.1 Specific Adverse Events

Kinase inhibition is often associated with cutaneous adverse events [19]. Among the 142 patients with advanced gastrointestinal stromal tumours treated with ripretinib 150 mg once daily in the phase I trial (NCT02571036), seborrhoeic keratosis was reported in 16.2% of patients and actinic keratosis was reported in 15.5% [10]. Furthermore, cutaneous squamous cell carcinomas developed in 7% of ripretinib recipients across the phase I trial and INVICTUS trial [20]. Dermatopathological analysis of biopsy samples from these skin lesions did not show aggressive histopathological features; lesions were manageable with local interventions without the need for dose modifications or interruptions.

Ripretinib weakly inhibits VEGFR2 [9], which may increase the risk to hypertension. In INVICTUS, hypertension was reported as a treatment related adverse event in 8% of ripretinib recipients versus 2% of placebo recipients [12]. Inhibition of the vascular endothelial growth factor signalling pathway also has the potential to slow wound healing, and a temporary interruption to ripretinib treatment before surgical procedures is recommended [7, 8].

Cardiac dysfunction is a common serious adverse event associated with other tyrosine kinase inhibitors [21]. There was a single instance of cardiac failure in the ripretinib group from the INVICTUS trial [12]. Ripretinib should be discontinued immediately in patients who develop grade 3 or 4 left ventricular systolic dysfunction [7, 8].

6 Dosage and Administration of Ripretinib

Ripretinib is approved for the treatment of adult patients with advanced gastrointestinal stromal tumours who have received prior treatment with three or more kinase inhibitors, including imatinib, in the EU [8], USA [7] and other countries around the world. The recommended dosage is 150 mg once daily taken orally at the same time each day with or without food. Dose interruptions or dose reductions may be required for adverse events. Ripretinib should be permanently discontinued in patients who are unable to tolerate a 100 mg dose once daily [7, 8].

No recommendations are available for patients with impaired kidney function with a creatinine clearance (Cl_cr) of 15–29 mL/min, as well as for patients with moderate to severe liver dysfunction [7, 8], although there is some evidence that moderate and severe hepatic impairment can increase ripretinib exposure by ~ 100% and 163%, respectively [22]. Local prescribing information should be consulted for detailed information regarding recommended dose modifications for adverse events, contraindications, potential drug interactions, use in special patient populations and warnings and precautions.

7 Current Status of Ripretinib in Advanced Gastrointestinal Stromal Tumours

The mutational status of the tumour plays a crucial role in determining the sensitivity of the cancer to a particular molecular-targeted therapy, with some mutants requiring changes to dosing or a different inhibitor entirely [23, 24]. Patients with tumours containing KIT exon 9 mutation benefit from a higher dose or a more frequent dose of imatinib. Further, tumours with a PDGFRα exon 18 D842V mutation are typically resistant to imatinib, and avapritinib instead of imatinib is recommended as the standard first-line therapy [23, 24]. Secondary resistance mutations that emerge can further add to the complexity of treating these tumours. Thus, activity against a broad spectrum of mutants is a likely requirement for an effective fourth-line treatment.

According to the ESMO-EURACAN-GENTURIS [23] and National Comprehensive Cancer Network (NCCN) [24] clinical practice guidelines, ripretinib 150 mg once daily is the recommended treatment for gastrointestinal stromal tumours after disease progression while on imatinib, sunitinib and regorafenib as the first, second and third lines of treatment, respectively. Ripretinib is also the only approved treatment in the USA and EU for this indication [7, 8], while in Japan the heat-shock protein 90 inhibitor pimespib recently gained approval for treatment of patients with gastrointestinal tumours who have failed chemotherapy and so is another fourth-line treatment option in Japan [25]. The NCCN guidelines also suggest that dose escalation to ripretinib 150 mg twice daily may be beneficial for patients who have progressed while on ripretinib 150 mg once daily [24].

Currently available clinical evidence supports the use of ripretinib as a fourth-line treatment. In INVICTUS, significant gains in progression-free survival and a favourable overall survival was seen in patients receiving ripretinib compared with placebo (Sect. 4). Patients included in the trial presented with a broad spectrum of activating and secondary resistance mutations [13]. Ripretinib had efficacy in the majority of these mutation profiles (Sect. 4), which can be attributed to its unique dual mechanism of action (Sect. 2).

Ripretinib had acceptable tolerability in patients with advanced gastrointestinal stromal tumours (Sect. 5). Generally, dose-limiting toxicities could be managed through dosage interruption and/or reduction. Many of
the treatment-emergent adverse events (diarrhoea, nausea, fatigue, myalgia, palmar-plantar erythrodysesthesia syndrome, hypertension and cardiac toxicities) are similar to those seen with other kinase inhibitors, such as imatinib and sunitinib [2, 24]. Compared with sunitinib, ripretinib was associated with a lower incidence of grade 3 or 4 treatment-emergent adverse events (Sect. 5) [18].

One of the limitations of the INVICTUS trial was that it had a relatively small number of participants and, as a result, lacked sufficient power to assess secondary endpoints or fully explore the impact of mutation subgroups (particularly for less common mutations (e.g. KIT exon 14, 18 and PDGFRA mutants)) on efficacy (Sect. 4). Additionally, because of the small numbers of participants, despite randomisation, there was a slight imbalance of baseline characteristics, including age of patients, between ripretinib and placebo groups [12].

In summary, ripretinib as fourth- or later-line therapy prolongs progression-free survival relative to placebo in patients with advanced gastrointestinal stromal tumours, with efficacy shown across a range of KIT and PDGFRA primary and secondary mutation profiles (Sect. 4). Ripretinib has acceptable tolerability (Sect. 5) and is currently the only approved fourth-line therapy for gastrointestinal stromal tumours in both the USA and EU. Ripretinib is therefore a valuable addition to the therapies used in the management of this disease.

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