Ripretinib (Qinlock®) for the treatment of patients with advanced gastrointestinal stromal tumour (GIST)

General information

Drug description [1]	Indication [2]
Ripretinib (Qinlock®, DCC-2618) is a switch-control tyrosine-kinase inhibitor (TKI) that broadly inhibits receptor tyrosine kinase (KIT) and platelet-derived growth factor receptor α (PDGFRA) kinase signalling through a dual mechanism of action.	Ripretinib (Qinlock®) is indicated for the treatment of adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib.

Current treatment [3]

- The following pharmacological treatment options for unresectable or metastatic GIST are recommended by NICE:
  - Imatinib as first-line management of people with KIT (CD117)-positive unresectable and/or KIT (CD117)-positive metastatic GIST.
  - Sunitinib as a treatment option for people with unresectable and/or metastatic GISTs that are imatinib-resistant or intolerant.
  - Regorafenib as a treatment option (third-line) for people with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, prior treatment with imatinib and sunitinib, only if their ECOG performance status is 0 to 1.
- In England, there are no other fourth-line therapies recommended by NICE for the treatment of patients with advanced GIST.
- ESMO guidelines also have no fourth-line therapy option however they do suggest rechallenge or continuation of treatment beyond progression with imatinib to which the patient has already been exposed.

Regulatory status

EMA	FDA [5]
Approval status for this indication: On 16 September 2021, the CHMP adopted a positive opinion, recommending the granting of a marketing authorisation for Qinlock®. **UPDATE:** Date of issue of marketing authorisation valid throughout the European Union: 18/11/2021 The full indication is: ❖ Qinlock® is indicated for the treatment of adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib. **Other indications**: none ✓ **Orphan status** ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 15 May 2020, the FDA approved ripretinib (Qinlock®) for adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib. **Other indications**: none

Costs

90 Qinlock® tablets 50 mg = € 21,500.00 (ex-factory price) [6]

Warnings and precautions

- **Palmar-plantar erythrodysesthesia syndrome:**
  - Based on severity, withhold Qinlock® and resume at the same or reduced dose.
- **New primary cutaneous malignancies**:
  - Perform dermatologic evaluations when initiating Qinlock® and routinely during treatment.
- **Hypertension**:
  - Do not initiate Qinlock® in patients with uncontrolled hypertension and monitor blood pressure during treatment.
  - Based on severity, withhold Qinlock® and then resume at same or reduced dose or permanently discontinue.

- **Cardiac dysfunction**:
  - Assess ejection fraction by echocardiogram or MUGA scan prior to initiating Qinlock® and during treatment, as clinically indicated.
  - Permanently discontinue Qinlock® for Grade 3 or 4 left ventricular systolic dysfunction.
- **Risk of impaired wound healing:**
  - Withhold Qinlock® for at least 1 week prior to elective surgery.
  - Do not administer for at least 2 weeks after major surgery and until adequate wound healing.
  - The safety of resumption of Qinlock® after resolution of wound healing complications has not been established.
- **Embryo-foetal toxicity:**
  - Can cause foetal harm. Advise females of reproductive potential of the potential risk to a foetus and to use effective contraception.
- **Phototoxicity:**
  - Ripretinib exhibits a potential for phototoxicity.
  - It is recommended to advise patients to avoid or minimise exposure to direct sunlight, sunlamps, and other sources of ultraviolet radiation due to the risk of phototoxicity associated with ripretinib. Patients should be instructed to use measures such as protective clothing (long sleeves and hat) and sunscreen with high sun protection factor.
- **CYP3A inhibitors and inducers:**
  - Ripretinib is a CYP3A substrate. Concurrent administration of ripretinib with the strong CYP3A and P-glycoprotein inhibitor itraconazole resulted in an increase in ripretinib plasma exposure. Caution is required when administering ripretinib with agents that are strong CYP3A and P-glycoprotein inhibitors.
  - Concurrent administration of ripretinib with the strong CYP3A inducer rifampicin resulted in a decrease in ripretinib plasma exposure. Therefore, chronic administration of agents that are strong or moderate CYP3A inducers with ripretinib should be avoided.
- **Important information about some excipients:**
  - Qinlock® contains lactose.
  - Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Study characteristics [1, 9, 10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
INVICTUS, DCC-2618-03-001 study) NCT03353753	129: 85 vs. 44	oral ripretinib 150 mg once a day + best supportive care	matching placebo once a day + best supportive care (crossover allowed[1])	PFS assessed by BICR	double-blind, randomised, placebo-controlled, phase 3 study	-	Deciphera Pharmaceuticals	[1]

Efficacy (I vs. C)

Primary analysis (data cut-off date 31 May 2019):
Median PFS by BICR: 6.3 months (95% CI 4.6–6.9) vs. 1.0 months (0.9–1.7); HR 0.15, 95% CI 0.09–0.25; p<0.0001
Patients who had progression or died: n=51/85 (60%) vs. n=37/44 (84%)
PFS at 6 months were estimated to be: 51% (39.4–61.4) vs. 3.2% (0.2–13.8)
Median PFS by investigator assessment: 4.7 months (95% CI 4.2–8.2) vs. 1.0 months (0.9–1.4); HR 0.19, 95% CI 0.12–0.32
Confirmed objective response: n=8/85 (9.4%; 95% CI 4.2–17.7) vs. n=0; median duration of response had not yet been reached (as of data cutoff), and n=1/8 responders had progressed; median time to best response: 1.9 months (IQR 1.0–2.7)

Safety (I vs. C)

Treatment-related serious AEs: n=8/85 (9%) vs. n=3/43 (7%)
Deaths[2]: n=12/85 (14%) vs. 13/43 (30%)
Treatment-related deaths: n=1 (1.2%) vs. n=1 (2.3%)
Discontinuation[3]: n=4/85 (4.7%) vs. n=1/43 (2.3%)

[1] Patients randomly assigned to placebo were permitted to **cross over** to ripretinib 150 mg at the time of disease progression. N=29/44 (66%) of patients in the placebo group crossed over to ripretinib at time of progression.
[2] **Ripretinib group**: 11 deaths due to disease progression and 1 death due to unknown reason; **placebo group**: 11 deaths due to disease progression and 2 deaths due to an adverse event (1 acute kidney injury, 1 septic shock).
[3] Treatment-related treatment-emergent AEs leading to study treatment discontinuation.

Median time to progression: 6.4 months (95% CI 4.6–8.4) vs. 1.0 month (0.9–1.7)
Median overall survival: 15.1 months (95% CI 12.3–15.1) vs. 6.6 months (4.1–11.6); HR 0.36, 95% CI 0.21–0.62), inclusive of the double-blind and open-label periods.
Patients who had died by the data cutoff: n=26/85 (31%) vs. n=26/44 (59%)
Estimated OS at 6 months: 84.3% (95% CI 74.5–90.6) vs. 55.9% (39.9–69.2)
Estimated OS at 12 months: 65.4% (51.6–76.1) vs. 25.9% (7.2–49.9)
QoL:

- Role and physical functioning (as assessed by EORTC-QLQ-C30) from baseline to cycle 2 day 1 remained stable in the ripretinib group with an adjusted mean change in score of 3.5 (95% CI –3.4 to 10.5) for role functioning and 1.6 (–2.5 to 5.7) for physical functioning, compared with a decrease with placebo of 17.1 for role functioning (95% CI –27.0 to –7.1) and a decrease of 8.9 for physical functioning (–14.8 to –3.0).
- Overall health (as assessed by EQ-VAS) from baseline to cycle 2 on day 1 also remained stable in the ripretinib group with adjusted mean change in scores of 3.7 (95% CI –1.1 to –8.6) compared with a decrease in the group that received a placebo of 8.9 (–15.9 to –1.9).
- Using either QoL instrument, the results showed a clinically relevant difference between ripretinib and placebo. Owing to hierarchal testing procedures of the endpoints, the QoL endpoint could not be formally tested for statistical significance.

INVICTUS efficacy results (as of 10 August 2020) [8]:
Median PFS: 6.3 months (95% CI, 4.6-8.1) vs. 1.0 months (95% CI, 0.9-1.7); HR 0.16 (95% CI, 0.10-0.27)
ORR (assessed by BICR): 11.8% (95% CI, 5.8-20.6) vs. 0 (95% CI, 0-8)
Median OS: 18.2 months (95% CI, 13.1-NE) vs. 6.3 months (95% CI, 4.1-10.0); HR 0.42 (95% CI, 0.27-0.67)

ESMO-MCBS version 1.1 [11]

Scale	Int.	Form	MG ST	MG	HR (95% CI)	Score calculation	PM	Toxicity	QoL	AJ	FM
Original	NC	2B	≤6 months	PFS: +5.3 months	0.15, (0.09-0.25)	HR≤0.65 AND gain ≥1.5 months	3	-	-	-	3
Adapted	NC	2B	≤6 months	PFS: +5.3 months	0.15, (0.09-0.25)	HR≤0.65 AND gain ≥1.5 months	3	-	-	-	3

Risk of bias (RCT) [12]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
yes	yes	yes	unclear[4]	yes[5]	unclear

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Abbreviations: AE=adverse event, AJ=adjustment, BICR=Blinded independent central review, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, ECOG=Eastern Cooperative Oncology Group, EMA=European Medicines Agency, EORTC-QLQ-C30=European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, EQ-VAS=EuroQol visual analogue scale, ESMO-MCBS= European Society of Medical

[4] The INVICTUS trial is ongoing until 04/2022. At the time of progressive disease by BICR, patients were unblinded and offered the option to continue or crossover to ripretinib open-label therapy.
[5] The study was designed by the funder with input from the investigators. Data collected by the investigators were analysed by the funder and interpreted jointly with all the authors. Medical writing assistance was provided by the sponsor.

Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, GIST=gastrointestinal stromal tumour, HR=hazard ratio, I=intervention, Int.=intention, KIT=receptor tyrosine kinase, MG=median gain, MUGA= multigated acquisition, n=number of patients, NICE=National Institute for Health and Care Excellence, OS=overall survival, PDGFRA=platelet-derived growth factor receptor α, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TKI=tyrosine-kinase inhibitor

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