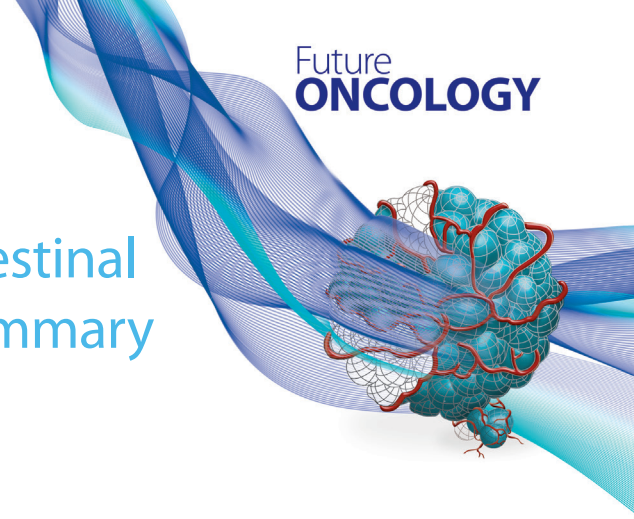
Future ONCOLOGY

Plain Language Summary of Publication

Ripretinib for advanced gastrointestinal stromal tumor: Plain language summary of the INVICTUS study



Marina Symcox[1] & Neeta Somaiah[2]
[1]Patient author; GIST Support International, Doylestown, PA, USA
[2]Sarcoma Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

First draft submitted: 28 June 2021; Accepted for publication: 22 September 2021; Published online: 18 October 2021

Summary

The purpose of this summary is to help you understand the results of the INVICTUS study originally published in the journal *Lancet Oncology*. INVICTUS is a clinical study which looked at **ripretinib** as a potential treatment for advanced gastrointestinal stromal tumor, also known as GIST. GIST is a type of cancer that starts in the digestive tract, also known as the gastrointestinal tract. In the study, all participants had advanced GIST and needed a fourth-line (or greater) treatment following the failures of three previous treatments. The study looked at how well **ripretinib** worked compared with a nonactive medicine (known as a placebo) and at the side effects. Participants were given **ripretinib** at a dose of 150 mg once a day or a placebo. The results of the INVICTUS study showed **ripretinib** increased the length of time participants survived before their cancer got worse. Treatment with **ripretinib** was associated with side effects that varied in severity. The results of this study led to **ripretinib**, also known by the brand name Qinlock®, being approved in the USA by regulators as the only medication for adults with advanced GIST who have previously been treated with 3 or more types of treatment called tyrosine kinase inhibitors.

How to say (double click to play sound)…
- **Ripretinib:** ri-pret-i-nib

Who should read this article?

This summary may be helpful for patients with GIST and their family members or caregivers. It may also be helpful for patient advocates and healthcare professionals.

Who sponsored the study?

This INVICTUS study was sponsored by Deciphera Pharmaceuticals, LLC, Waltham, MA, USA.

What is advanced gastrointestinal stromal tumor?

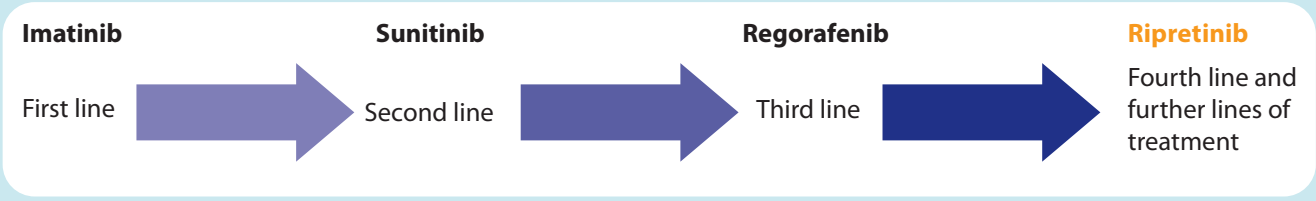
Gastrointestinal stromal tumor (also called GIST) is the most common sarcoma (a type of cancer that develops in bone or soft tissue) of the gastrointestinal tract. It is frequently found in the stomach or small intestine but can start anywhere along the digestive tract. Small tumors may go undetected, as they typically do not cause any symptoms. However, larger tumors or more advanced GISTs do cause symptoms, and these include abdominal pain, nausea and vomiting, feeling full after only eating a small amount, abdominal swelling, and blood in the vomit or stool.

Advanced GISTs (tumors that have grown larger or have spread to another part of the body) are unlikely to be cured. In patients with advanced GIST, surgery to remove the tumor may not be an option, and patients are given drugs to treat their cancer.

Future Medicine part of fsg

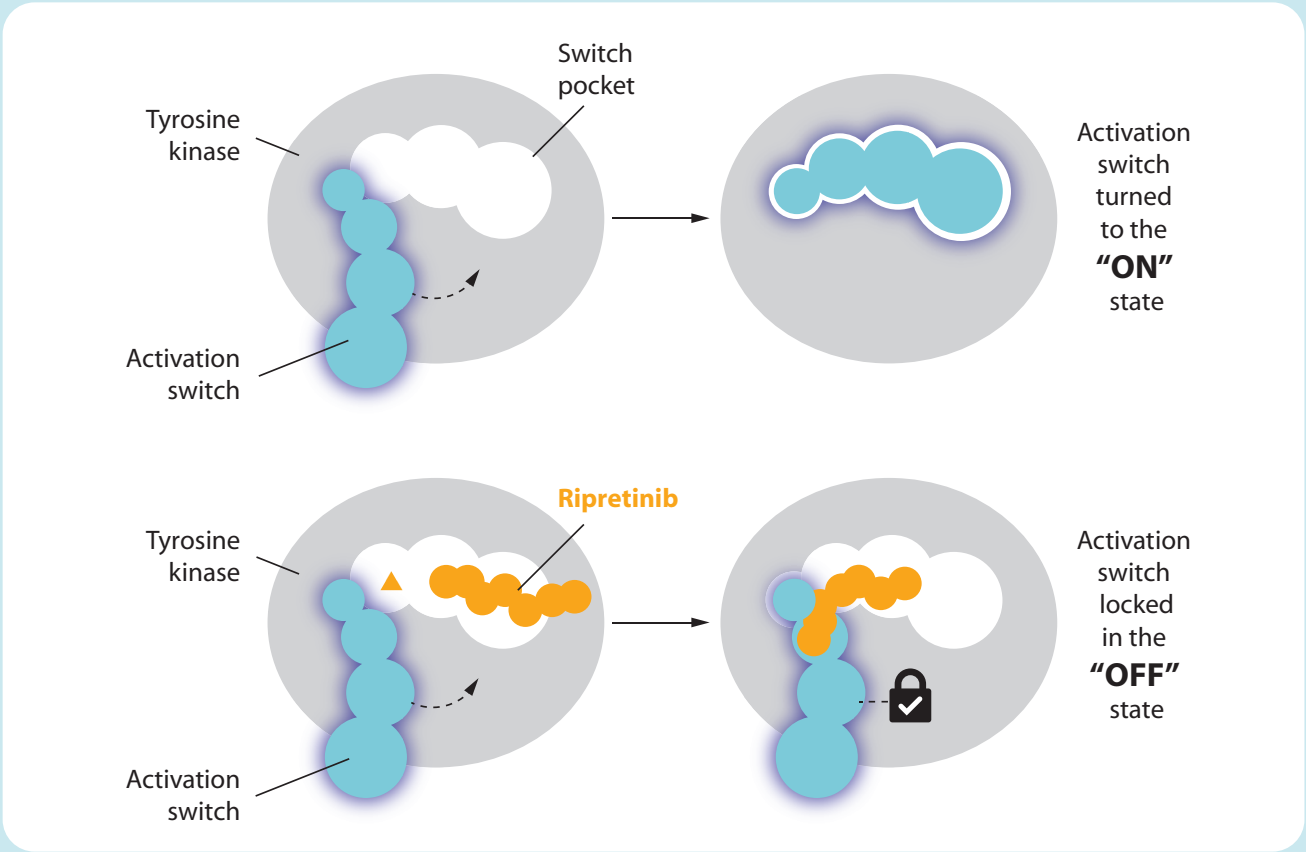
What is advanced gastrointestinal stromal tumor? (continued)

Initial treatment for cancer is called first-line therapy. The approved first-line therapy for GIST is imatinib (also called Gleevec®). First-line therapy sometimes doesn't work, stops working, or causes serious side effects, so patients are given different treatment options. Patients can then be given the approved second-line treatment sunitinib (also known as Sutent®) and then receive the approved third-line treatment regorafenib (also called Stivarga®).



These therapies inhibit KIT and PDGFα receptors. KIT and PDGFα receptors are proteins that can be turned on when other molecules (ligands) bind to them. When they are on, they can turn on other proteins, which ultimately leads to cell growth. When these proteins become altered through changes in the genes that encode for them (mutations), they turn on when they should be off. This can result in abnormal cell growth and lead to the development of tumors. Other drugs approved to treat GIST help to keep these altered proteins turned off, but over time, new alterations or mutations occur that make these proteins resistant to the treatment, and tumor growth resumes.

Ripretinib works differently compared with previous lines of therapy and binds to the switch that is responsible for turning the protein on.



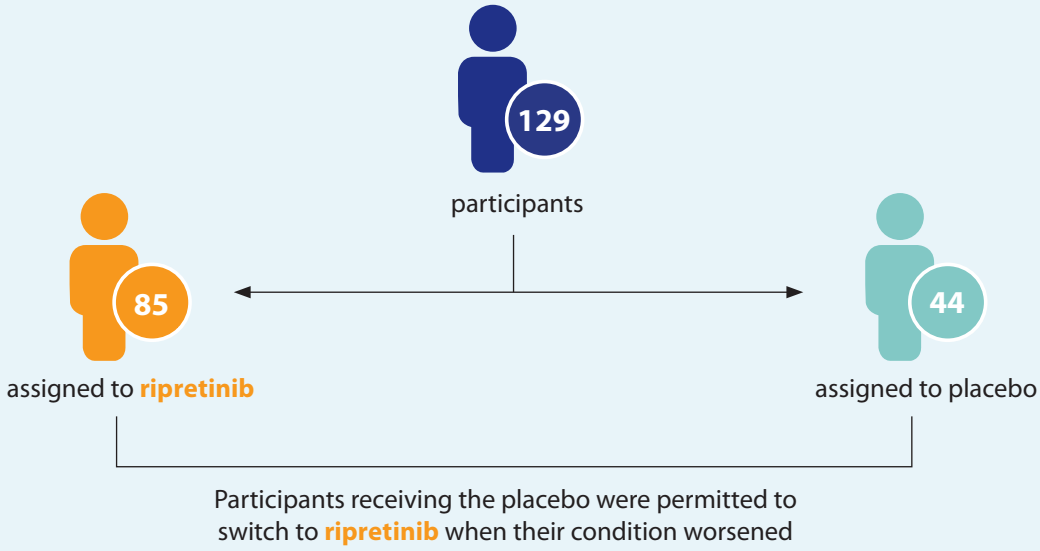
What was the purpose of the study?

- The INVICTUS study investigated **ripretinib** as a treatment for patients with advanced GIST who needed a fourth (or greater) line of therapy
- The main aim of the study was to see if treatment with **ripretinib** could affect tumor growth and extend survival time compared with placebo treatment (a pill with no active ingredient)

Who took part in the study?

The INVICTUS study included 129 participants aged 18 and older.

It was randomly decided whether participants were given the study drug (**ripretinib**) or placebo. 85 participants were assigned to and received **ripretinib**, and 44 participants were assigned to receive placebo, but 1 did not take it.

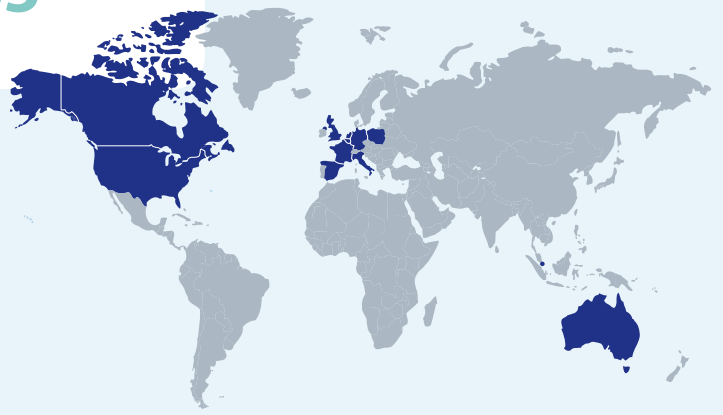


All participants met the following criteria:

- ✓ Confirmed diagnosis of GIST
- ✓ At least one measurable tumor
- ✓ Progressed on at least the first 3 lines of therapy: imatinib (Gleevec®), sunitinib (Sutent®), and regorafenib (Stivarga®)
  - Many participants (37%) received more than 3 previous therapies
- ✓ An Eastern Cooperative Oncology Group (ECOG) score of 0–2
  - The ECOG scale measures how the disease impacts daily living; possible scores range from 0 (fully active with no restrictions) to 5 (dead)

Characteristics of participants in the study

- The median age for participants receiving **ripretinib** was **59 years**
- The median age for participants receiving placebo was **65 years**
- Together, **75%** of the participants were white

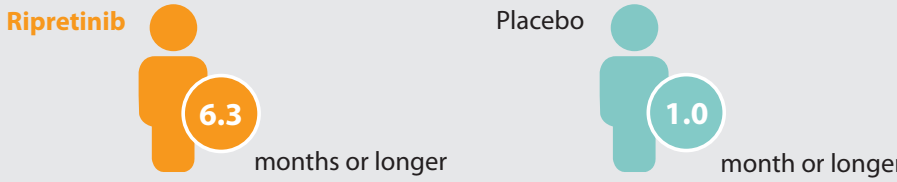


The INVICTUS study took place in 29 hospitals in 12 countries, including the following:

United States	13	Canada	1
United Kingdom	2	Poland	1
Spain	2	Belgium	1
France	2	The Netherlands	1
Germany	2	Australia	1
Italy	2	Singapore	1

What were the overall results of the study?

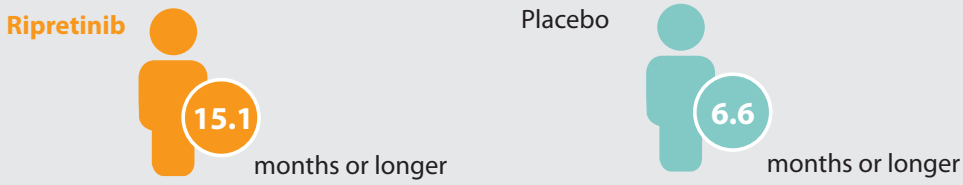
Half of the participants receiving **ripretinib** survived for 6.3 months or longer before their cancer got worse, compared with 1.0 month or longer for participants receiving placebo



Of the 85 participants receiving **ripretinib**, 8 had partial responses – meaning that the size of their tumor was reduced by 30% or more (as defined in a set of rules called modified Response Evaluation Criteria in Solid Tumors [mRECIST])

- After the responses were analyzed, they were not considered statistically conclusive

Half of the participants receiving **ripretinib** survived overall for 15.1 months or longer from the start of therapy, compared with 6.6 months or longer for participants receiving placebo; this included participants on placebo who were permitted to take **ripretinib** when their disease worsened



On questionnaires that investigated quality of life, participants receiving **ripretinib** had stable scores after their first cycle of treatment, while participants receiving placebo reported a decline in quality of life

- These questionnaires included evaluations of physical function, everyday capabilities, and patient perceptions of their overall health and quality of life

What were the most common side effects?

In the study, participants experienced **treatment-emergent side effects** that were related to treatment. These are side effects that occur after starting treatment that are caused by the medication. The most common side effects for participants who received **ripretinib** were as follows:

Hair loss

49%
(42 out of 85 participants)

Muscle aches/pains

28%
(24 out of 85 participants)

Nausea

26%
(22 out of 85 participants)

Fatigue

26%
(22 out of 85 participants)

Hand-foot syndrome*

21%
(18 out of 85 participants)

Diarrhea

21%
(18 out of 85 participants)

Constipation

15%
(13 out of 85 participants)

Decreased appetite

15%
(13 out of 85 participants)

*Redness, pain, swelling, and blistering on the palms of the hands and soles of the feet

Serious treatment-related side effects (adverse events that were life-threatening and resulted in hospitalization or death) were reported in 9% (8 out of 85) of participants taking **ripretinib** and included the following:


9%
(8 out of 85 participants)

- Decreased red blood cells
- Heart failure
- Death of unknown cause
- Trouble breathing
- Hardened impacted stool
- Gastro-esophageal reflux disease
- High potassium in the blood
- Low phosphate in the blood
- Nausea
- Upper gastrointestinal bleeding

Serious treatment-related side effects were also reported in participants receiving **placebo** and included the following:


7%
(3 out of 43 participants)

- High potassium in the blood
- Dehydration
- Excess fluid in the lungs
- Septic shock

Of the 85 participants who received **ripretinib**, 12 (14%) died:


14%
(12 out of 85 participants)

- 11 due to disease progression
- 1 unknown cause

Of the 43 participants who received the **placebo**, 13 (30%) died:


30%
(13 out of 43 participants)

- 11 due to disease progression
- 1 due to an unrelated side effect (acute kidney injury)
- 1 due to a treatment-related event (septic shock/pulmonary edema)

What do the results of this study mean?

- The results of this study showed that **ripretinib** provides a viable treatment option for patients with GIST who have already tried 3 or more different therapies.
- **Ripretinib** therapy is associated with some treatment-emergent side effects that are generally well controlled, and the results suggest participants of this study were able to maintain their everyday functioning (quality of life) on treatment.
- The approval of **ripretinib**, based on the results of this study, led to a change in the treatment guidelines, with **ripretinib** acting as the standard of care for fourth-line therapy in patients with advanced GIST.
- **Now patients have an approved treatment option following the failure of 3 or more therapies.**

Where can readers find more information on this study?

The full title of the original publication is 'Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial' and was published in *Lancet Oncology*. You can read the abstract of the original article at:
https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(20)30168-6/fulltext
Accessing this paper and its supplemental material requires a small fee.

You can read more about the INVICTUS study on the following websites:
- Type the trial number, NCT03353753, into the search bar of the Clinicaltrials.gov website (www.clinicaltrials.gov)
- For more information on **ripretinib**, please visit www.qinlock.com

Patients should ask their healthcare providers for more information about treatment with **ripretinib** to find out if **ripretinib** is right for them.

Educational resources

- Read more about GIST at the American Cancer Society website: https://www.cancer.org/cancer/gastrointestinal-stromal-tumor.html
- Read the NCCN patient guidelines for treatment of soft tissue sarcoma, which includes treatment of GIST, at: https://www.nccn.org/patients/guidelines/content/PDF/sarcoma-patient.pdf
- Find resources and support at: https://www.gistsupport.org/
- Find specific information about mutation testing at: https://www.gistsupport.org/about-gist/for-new-gist-pages/mutation-testing/
- Find financial resources for **ripretinib** treatment at: https://www.decipheraaccesspoint.com/

Acknowledgments

The authors and sponsor would like to thank the patients, their families and caregivers, the investigators, and the investigational site staff of the INVICTUS study. Writing and editorial support were provided by Lauren Hanlon, PhD, of AlphaBioCom, LLC, King of Prussia, PA, USA, and funded by Deciphera Pharmaceuticals, LLC.

Financial & competing interests disclosure

M Symcox owns stock in Deciphera Pharmaceuticals and Blueprint Medicines. N Somaiah serves in an advisory/consultancy role for Deciphera Pharmaceuticals, Bayer, Blueprint Medicines, and Boehringer Ingelheim; has received research funding from Deciphera Pharmaceuticals, Ascentage, Daiichi Sankyo, AstraZeneca, GlaxoSmithKline, and Karyopharm; and has an immediate family member who owns stock in Pfizer.