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.

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.
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 PDGF\(\alpha\) receptors. KIT and PDGF\(\alpha\) 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 is advanced gastrointestinal stromal tumor? (continued)**

*Tyrosine kinase*

*Switch pocket*

*Activation switch*

*Activation switch turned to the “ON” state*

*Activation switch locked in the “OFF” state*
Ripretinib for advanced gastrointestinal stromal tumor: the INVICTUS study

Plain Language Summary of Publication

**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.

Participants receiving the placebo were permitted to switch to ripretinib when their condition worsened.

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
- United Kingdom: 2
- Spain: 2
- France: 2
- Germany: 2
- Italy: 2
- Canada: 1
- Poland: 1
- Belgium: 1
- The Netherlands: 1
- Australia: 1
- 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:

- 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:

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

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

- 11 due to disease progression
- 1 unknown cause

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

- 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.