Life Fest 2024

SAN JOSÉ

California

GIST 101: Introductions to the Biology & Medical Treatment of GIST

David Josephy, PhD

President, GIST Sarcoma LRG Canada

Introduction to the Biology and Medical Treatment of GIST

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David Josephy
Life Raft Group Canada

david.josephy@liferaftgroup.ca

Disclaimers:

I am a retired scientist (biochemistry/ toxicology) with some experience in cancer research. I am not a physician and I cannot provide medical advice.

In biology and medicine, there are exceptions to almost every rule; some of the statements in this presentation are simplified, for clarity.

GIST "Top ten" list

1. GIST strikes randomly – getting GIST was not your fault.

2. Unlike the common GI tract cancers, GISTs are very treatable.

3. GISTs are rare! Find a GIST specialist.

4. Ask whether your GIST is 'localized' or has 'metastasized' (spread).

5. Get a copy of your pathology report.

6. Ask for mutational testing of the tumor to be done.

7. For localized GIST: 'adjuvant' imatinib can reduce the risk of recurrence.

8. Four oral ('take-home') drugs are approved for GIST.

9. Side effects of GIST drugs can be managed successfully, in most cases.

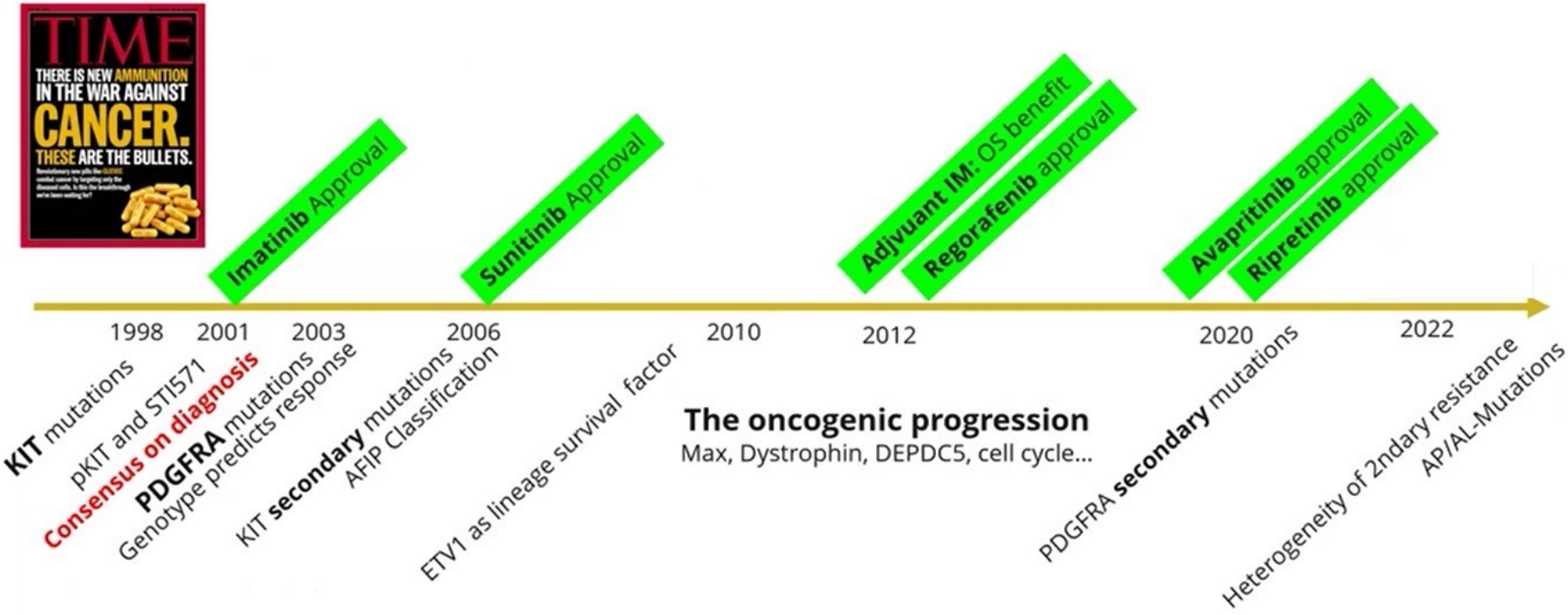
10. Reach out! Join a support group such as Life Raft Group.

TOPICS

- What causes GIST?
- What are “ICCs” – the cells where GISTs start?
- What is KIT?
- How does mutational testing differ from IHC?
- What are the existing “TKI” drugs for GIST?
- What are the prospects for new drugs?

Milestones in GIST research and treatment 1998-present

Information from before 2000 is irrelevant.
Later information, too, is rapidly being overtaken by advances.
Looking at survival statistics means looking back in time.



(courtesy of Dr Sebastian Bauer)

A note about "SDH-deficient" GIST

Since about 2010, we have known that a sub-set of GISTs are deficient in expression of the enzyme complex succinate dehydrogenase (SDH: "Complex II of the electron transport chain", for those who have taken a biochemistry course).

SDH-deficient GISTs have very different biology and treatment.

A separate "track" of this meeting focuses on SDH-deficient GIST. Most of my presentation does not apply to SDH-deficient GIST.

What causes GIST?

GISTs occur "sporadically", as a result of random mutations; GIST is not inherited from one's parents and cannot be passed on to one's children*.

No environmental, occupational, dietary, lifestyle, ethnic, or geographical causes of GIST are known – and *if there were any substantial risk factors, they would surely have been identified by now*.

***There are very rare exceptions to this rule: germline (heritable) mutations in the genes *SDH*, *KIT*, and *PDGFRA* are known (Pantaleo *et al.*, *Front. Oncol.* 2022; Yan *et al.*, *Oncologist* 2023).**

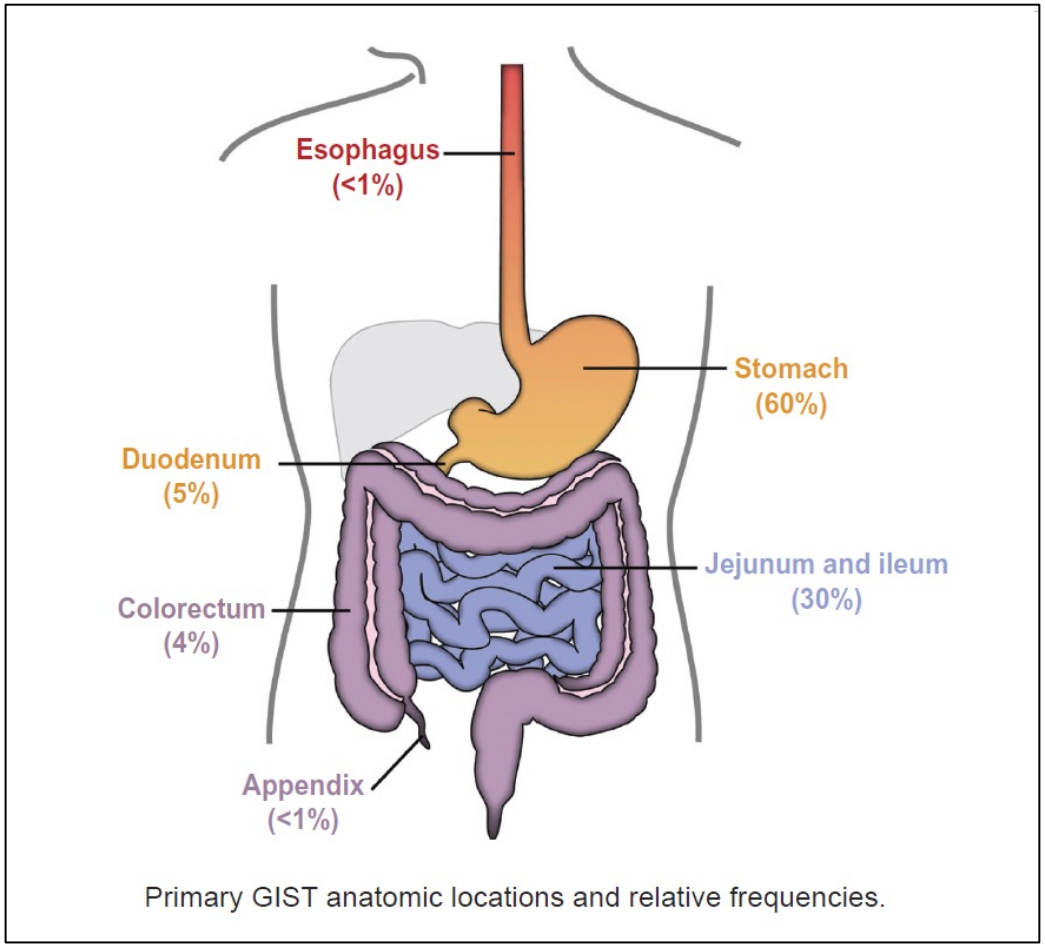
Carcinomas *vs.* sarcomas

***Carcinomas** are cancers that arise in **epithelial** tissues, such as the skin and the tissues that line the organs. Carcinomas are the most common cancers of the skin, breast, colon, prostate, lung, stomach, etc.*

***Sarcomas** are cancers that arise in **connective** and **supportive** tissues. Examples: osteosarcoma (bone); liposarcoma (fat); angiosarcoma (blood vessels).*

Sarcomas are rare (only about 1% of adult cancers).

GIST is a sarcoma of the gastrointestinal tract.

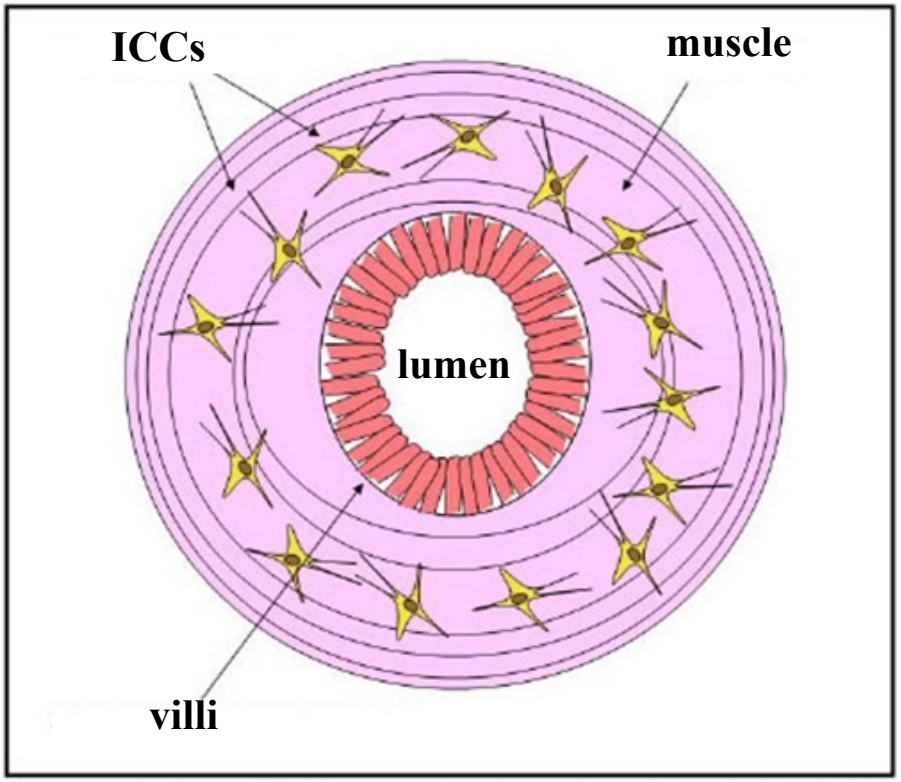


Primary GIST anatomic locations and relative frequencies.

Foo, Liegl-Atzwanger, and Lazar, *Clinical Medicine Insights: Pathology* 2012

GI carcinomas (esophagus, stomach, colon) are common.
GI sarcomas (GISTs) are rare.

Interstitial Cells of Cajal: the cells where GISTs start; the "pacemaker" cells that coordinate GI peristalsis.

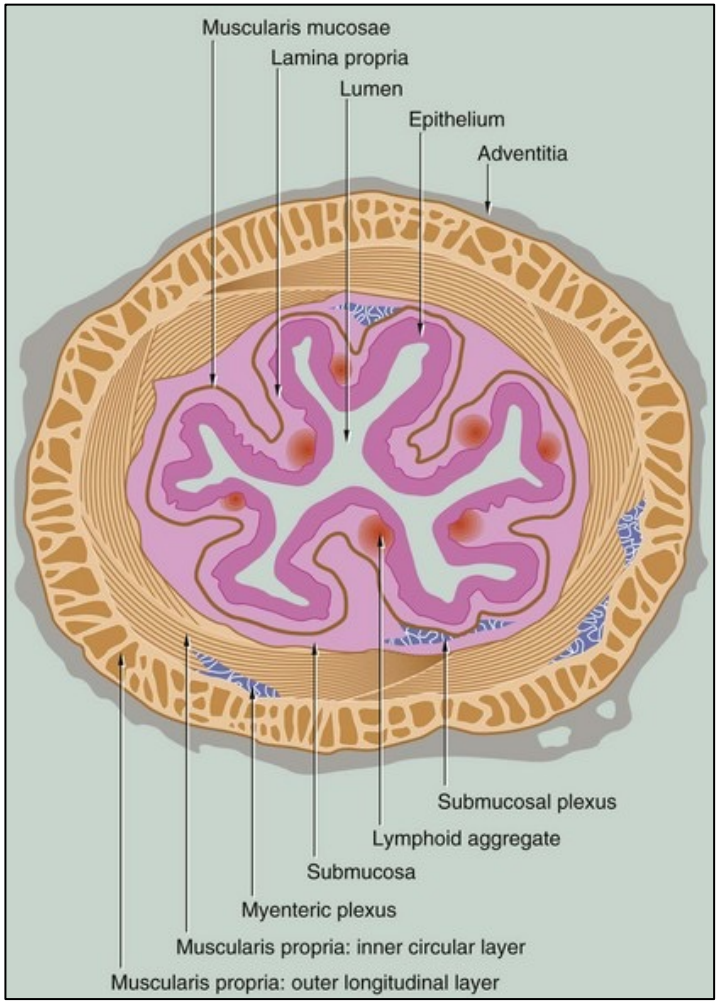


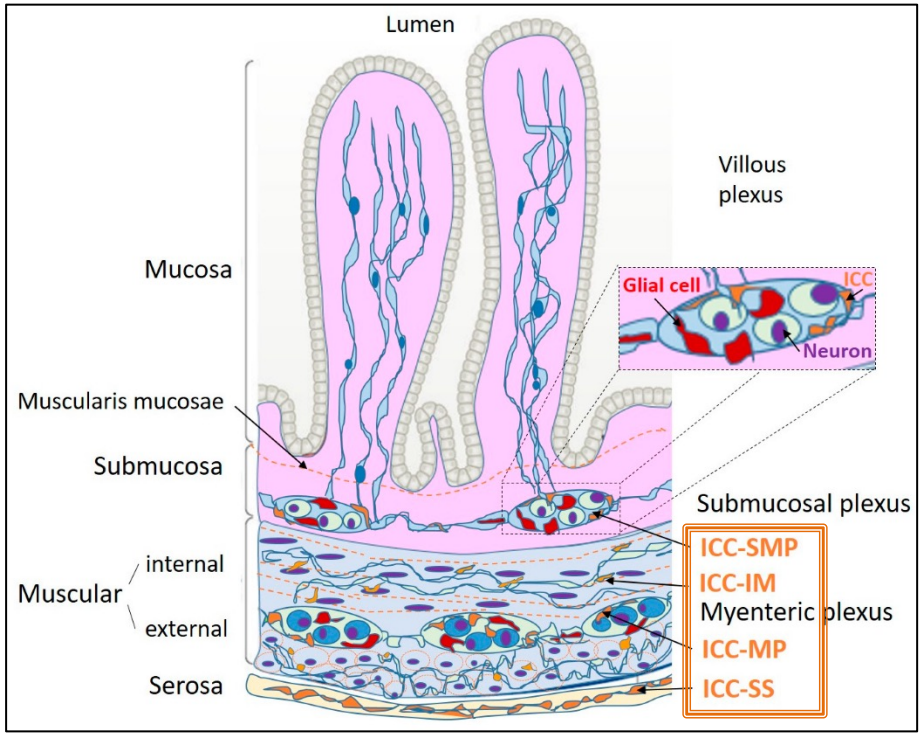
Cajal (1852-1934)

Huizinga *et al.*, Interstitial cells of Cajal and human colon motility in health and disease, *Am. J. Physiol. Gastrointest. Liver Physiol.* (2021)

Carcinomas (*e.g.* the common stomach and colon carcinomas) start in the g.i. tract epithelium.

GISTs are sarcomas; they start in the muscular wall.





López-Pingarrón *et al.*, *Curr. Issues Mol. Biol.* (2023)

Oncogenes

Oncogenes are human genes which, when mutated, can drive the development of a cancer.

Oncogenes encode proteins that act as cellular "gas pedals" or "master switches"- *when they receive an appropriate signal*, they "step on the gas" and instruct the cell to divide/ proliferate.

(Regulated cell division is a normal, essential process for growth and development, maintenance, wound repair, etc.)

Mutant oncogenes encode aberrant proteins that act like "gas pedals stuck to the floor", driving unregulated cell division.

Dozens of human oncogenes are known: *BRAF*, *EGFR*, *HRAS*, *PTEN* …

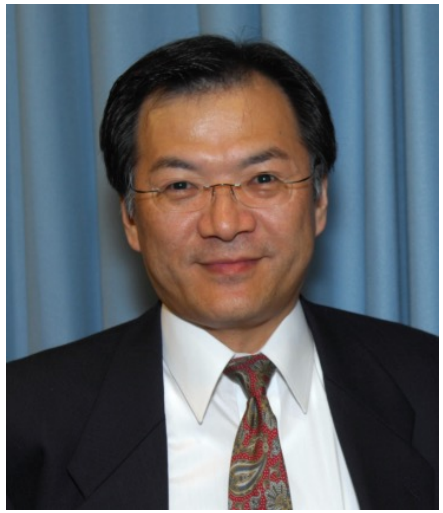
Specific oncogenes *tend* to be associated with specific cancer types.

The therapeutic concept: Disable the gas pedal!

GIST and the *KIT* gene: the 1998 breakthrough that revolutionized GIST diagnosis and treatment.

- GIST cells almost always express a protein called "KIT"
  (very few other cells in the body do so)

- In most GISTs, the *KIT* oncogene is mutated.



Yukihiko Kitamura, M.D. Seiichi Hirota, M.D.

Osaka University Medical School

KIT (for “kitten”!)

The *KIT* oncogene was discovered in basic cancer research studies, in the late 1980s (Chabot *et al.*, *Nature 335: 88-89*, 1988).

The name “kit” refers to the fact that the gene was discovered as a gene from a virus that causes *sarcomas in cats*: HZ4 feline sarcoma virus. A closely related gene is found in the mammalian genome.

(In fact, many oncogenes were discovered as viral genes and only later recognized as being closely related to human genes.)

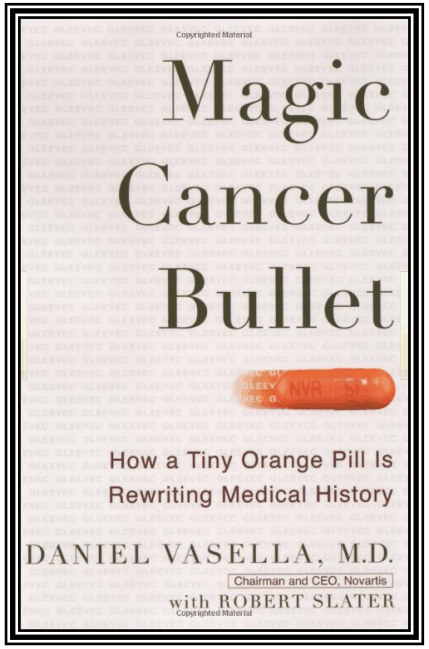
The connection between KIT and GIST was not recognized until the work of Kitamura and Hirota, a decade after KIT was discovered.

Oncogenes and targeted cancer therapies

Imatinib was one of the first drugs targeting the protein product of an oncogene (ABL); it was first used for the treatment of CML (chronic myelogenous leukemia), in 1998, with immediate and amazing results.

Dr. Brian J. Druker

May 28, 2001



Oncogenes: targeted therapy for GIST

1998: Most GISTs are driven by mutations in the *KIT* gene.

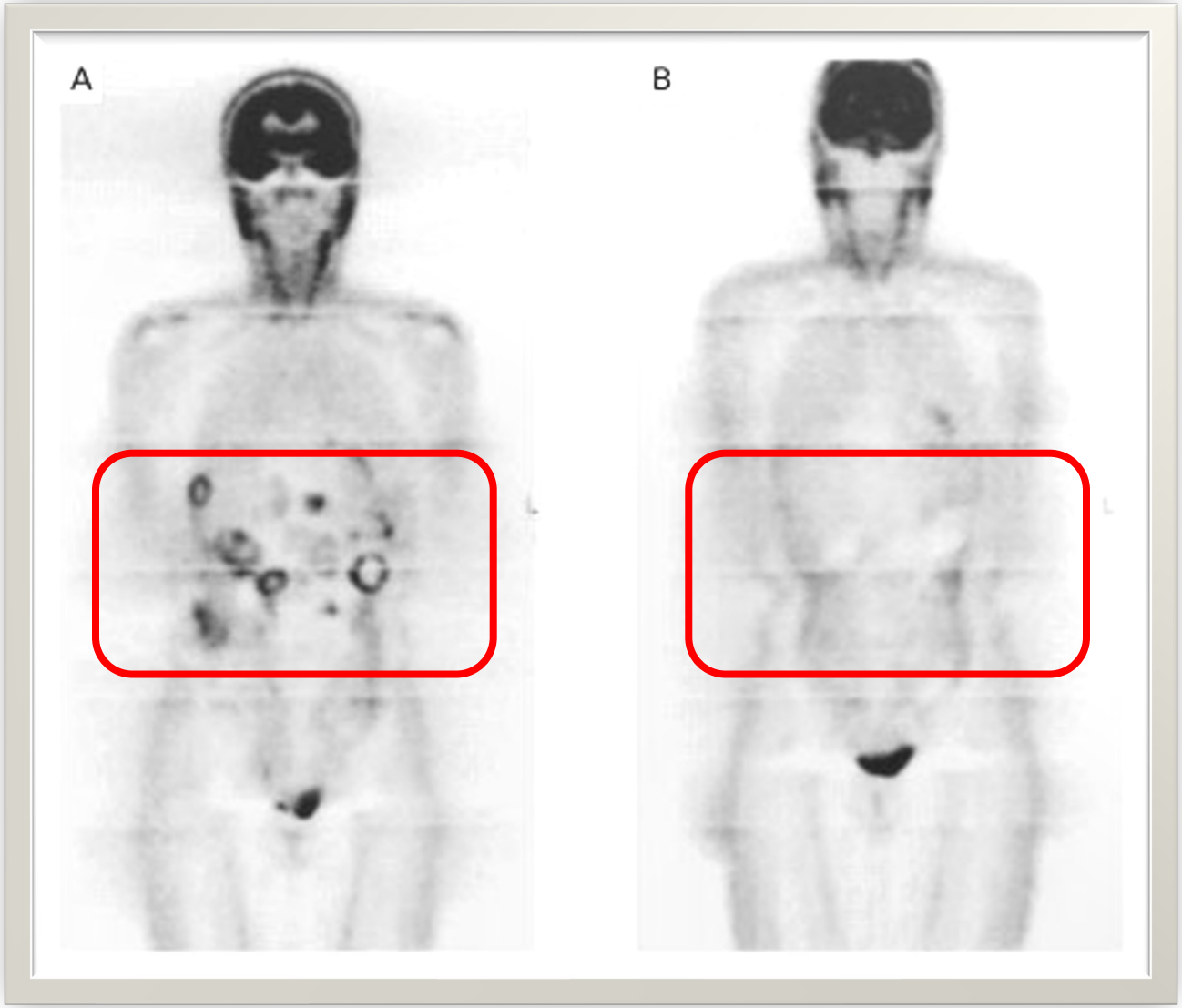
This research showed – unexpectedly – that GIST has similarity with CML – a completely different cancer – at the genetic/ molecular level.

CML is driven by the *ABL* oncogene.
GIST is driven by the *KIT* oncogene.
***ABL* and *KIT* are "cousins".**

1998: Imatinib used for the treatment of CML.

2000: Dr. Joensuu (Finland) and Dr. Demetri (Boston, USA) decided to treat a GIST patient with imatinib.

Imatinib (Gleevec - Novartis)



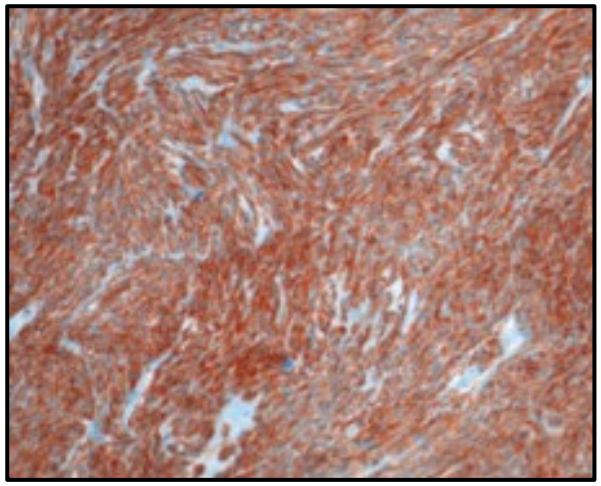
Joensuu *et al.*, *N. Engl. J. Med.* 344: 1052-1056, 2001.

KIT (also called "c-Kit" or "CD117")

The KIT protein is made (expressed) by only a few types of adult cells, including the Interstitial Cells of Cajal … and GISTs.

Immunohistochemistry (IHC):

The essential step in diagnosing GIST is to test whether the tumor cells express KIT protein. The test is performed by *staining* a slice of the tissue sample (obtained at surgery) with an *antibody* that recognizes KIT protein.



Di Vizio *et al.*, 2008

A pathologist examines the stained tissue under the microscope. If the cells stain brown, they are almost certainly GIST.

Immunohistochemistry (IHC) *vs.* Mutational testing:
different tests, different questions, different answers

	Immunohistochemistry	Mutational testing
What it is:	**Staining for the KIT protein**	**DNA sequencing of the *KIT* gene**
What it tests for:	**expression of KIT protein by the tumour cells**	**mutations in the *KIT* gene in the tumour cell DNA**
What it tells us:	**is the tumour GIST? (often, this simply confirms the diagnosis)**	**is the tumour a *KIT*-mutant GIST (and, if so, what is the *KIT* mutation?)***
What it requires:	**a tumour sample (biopsy or surgery)**	**a tumour sample (*e.g.*, FFPE: Formalin-Fixed Paraffin-Embedded)**
Will the test be performed by the pathology lab?	***always***	***sometimes*; LRG strongly recommends that patients push to have mutational testing done!**

*If no mutation is found in the *KIT* gene, the lab will probably go on to examine other genes, *e.g. PDGFR*, *RAS*, *BRAF* …

GIST Drugs: Imatinib and beyond

The first three TKIs approved for use in GIST:

(The 'ib" ending indicates that the drug is an enzyme inhibitor.)

1st-line: Imatinib (Gleevec – Novartis; 2001)

2nd-line: Sunitinib (Sutent – Pfizer; 2006)

3rd-line: Regorafenib (Stivarga – Bayer; 2013)

All of these drugs act by the same mechanism – blocking the binding of ATP (cellular fuel) to KIT.

The fourth TKI approved for use in GIST:

4th-line: Ripretinib (Qinlock – Deciphera/Ono; 2020)

Ripretinib acts on KIT by a different mechanism – locking the protein in its inactive state ("switch-pocket" inhibitor).

The fifth TKI approved for use in GIST:

5th-line: Avapritinib (Ayvakit – Blueprint; 2020)

For PDGFRA-D842V GIST *only*.

"GIST patients do well … until they *don't* do well … and then, they don't do well."

The usual treatment paradigm for metastatic GIST is:

- **imatinib, until progression**

→ imatinib dose escalation, if possible

→ switch to sunitinib, until progression

→ switch to regorafenib, until progression …

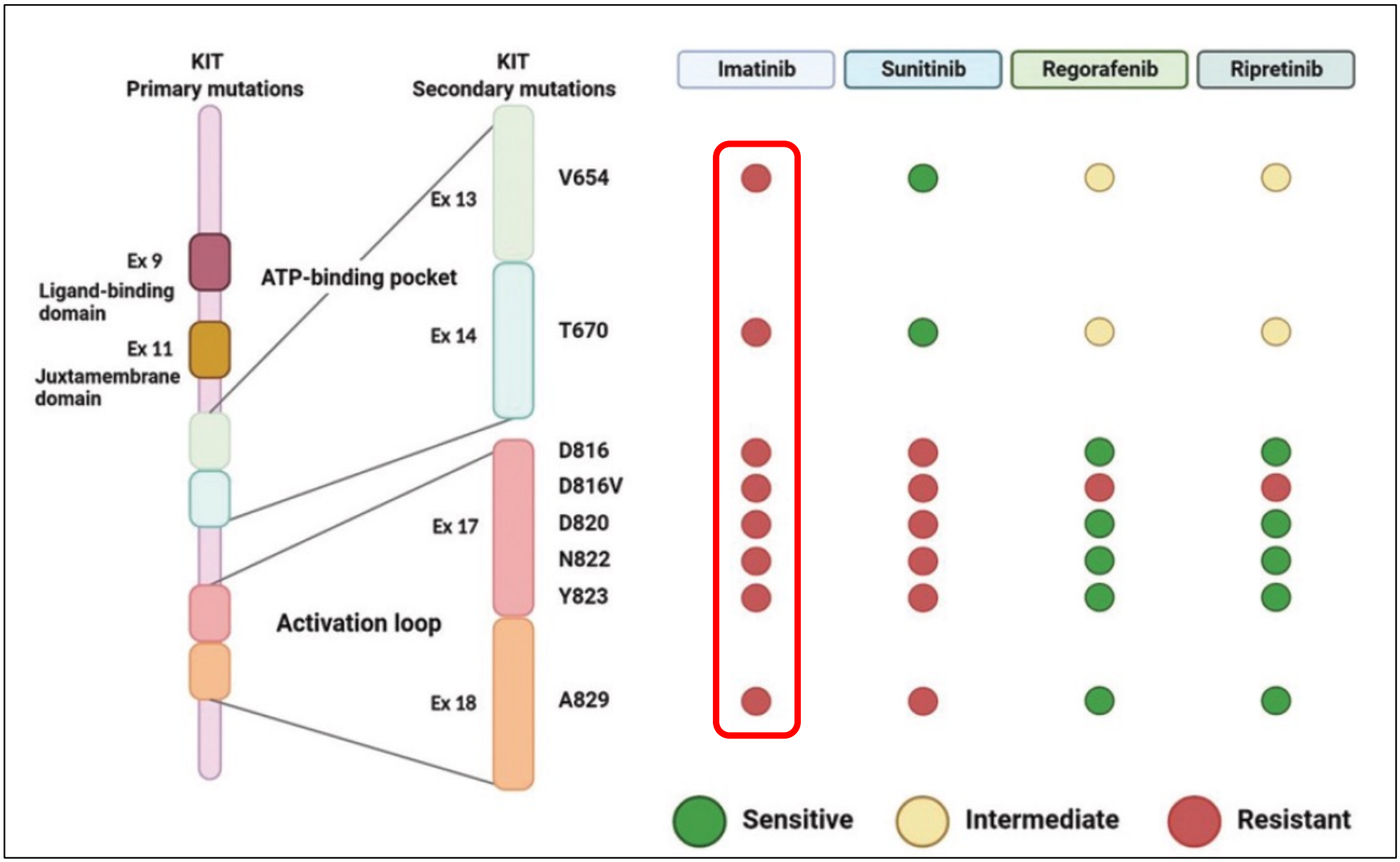
"When I am referred a GIST patient because he or she has progressed while on imatinib, I first stop and ask:

- Was it really a GIST?
(misdiagnosis??)

- Was it really progression
(misinterpretation of radiology results??)

- Was the patient really taking the drug?
(*non-compliance??*)"

Imatinib resistance: secondary mutations in *KIT*



Cicala *et al.*, *Expert Opin. Investig. Drugs*, 2024

More drugs are needed:

- **Some GISTs are imatinib-resistant from the outset.**
- **Tolerance of the drugs (side effects) is variable.**
- **TKIs halt the growth of most GISTs, but do not eliminate them; over time, *GIST tumours tend to become TKI-resistant, mainly due to additional mutations arising in the metastases*.**
- **The imatinib dose may be increased, followed by switching to sunitinib, etc. Unfortunately, development of TKI resistance limits the usefulness of all of the drugs.**

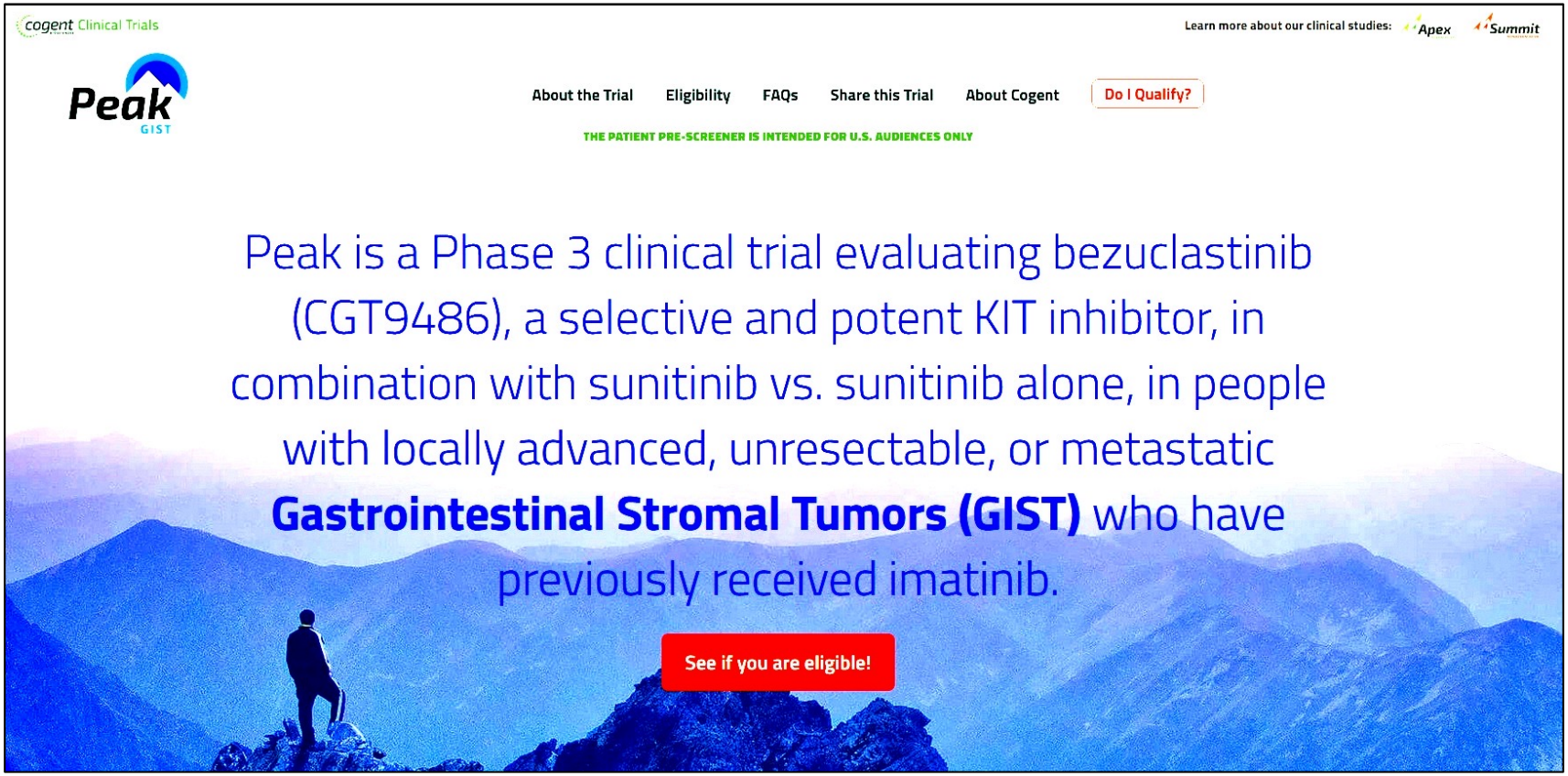
New KIT inhibitors for GIST - in clinical trials, 2024

NB003 (formerly AZD3229 – AstraZeneca): Ningbo Newbay

IDRX-42: IDRx, Inc.

Bezuclastinib (formerly PLX 9486 – Plexxikon): Cogent

Bezuclastinib



Possible novel strategies against advanced GIST:

- **New TKIs**
  - **more potent**
  - **tailor-made for secondary mutations such as D816V**

- **Combinations of TKIs**

- **Attacking the KIT signaling pathway further 'downstream' (*e.g.* MEK inhibitors)**

- **Non-TKI therapies, *e.g.* immuno-oncology**

- **Improving local treatments, *e.g.* radiofrequency ablation**

All of these avenues are being explored.