GIST Life Raft Group Canada; Day of Learning; Toronto; Oct. 29, 2022

GIST Treatment: updates

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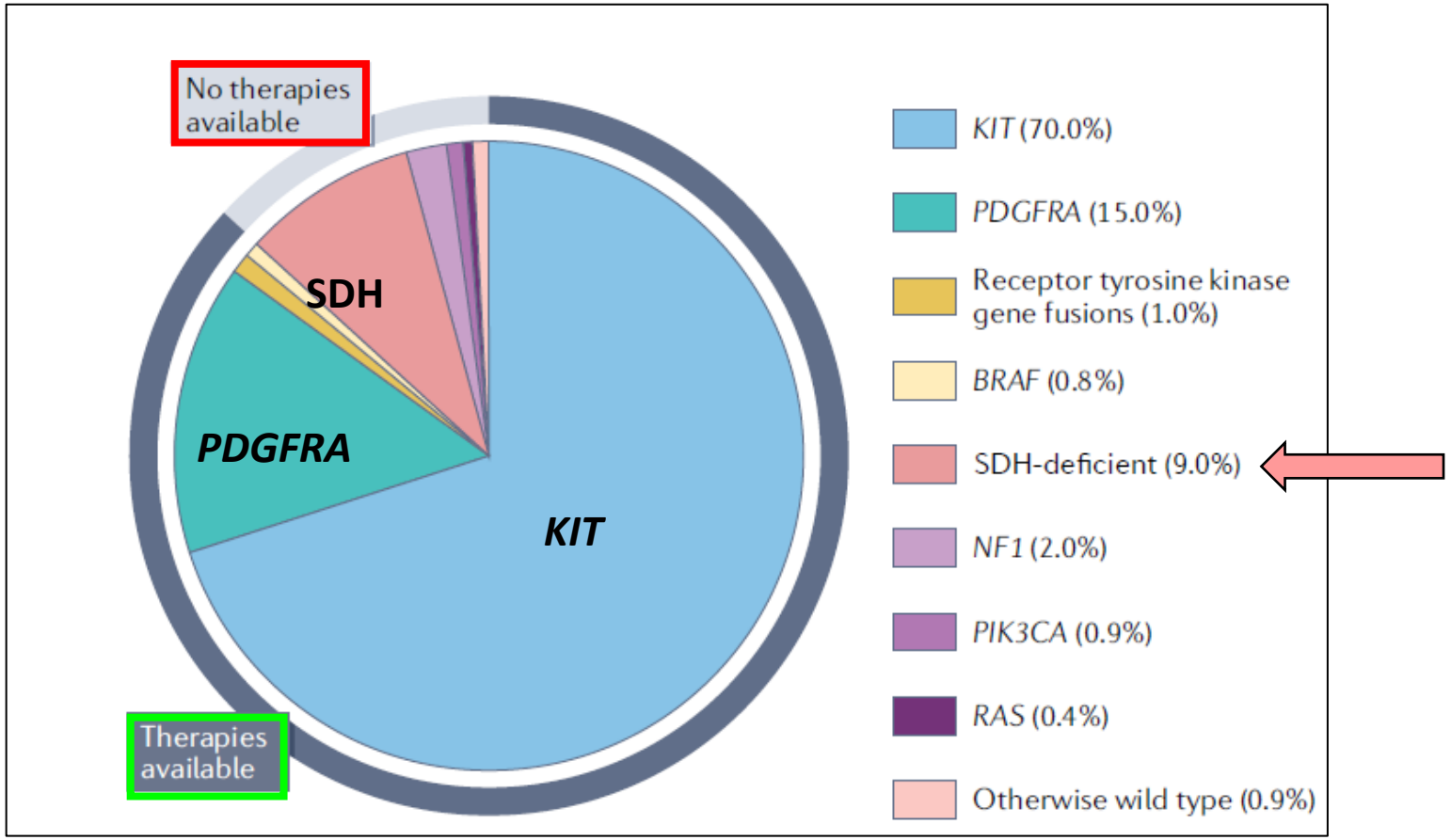
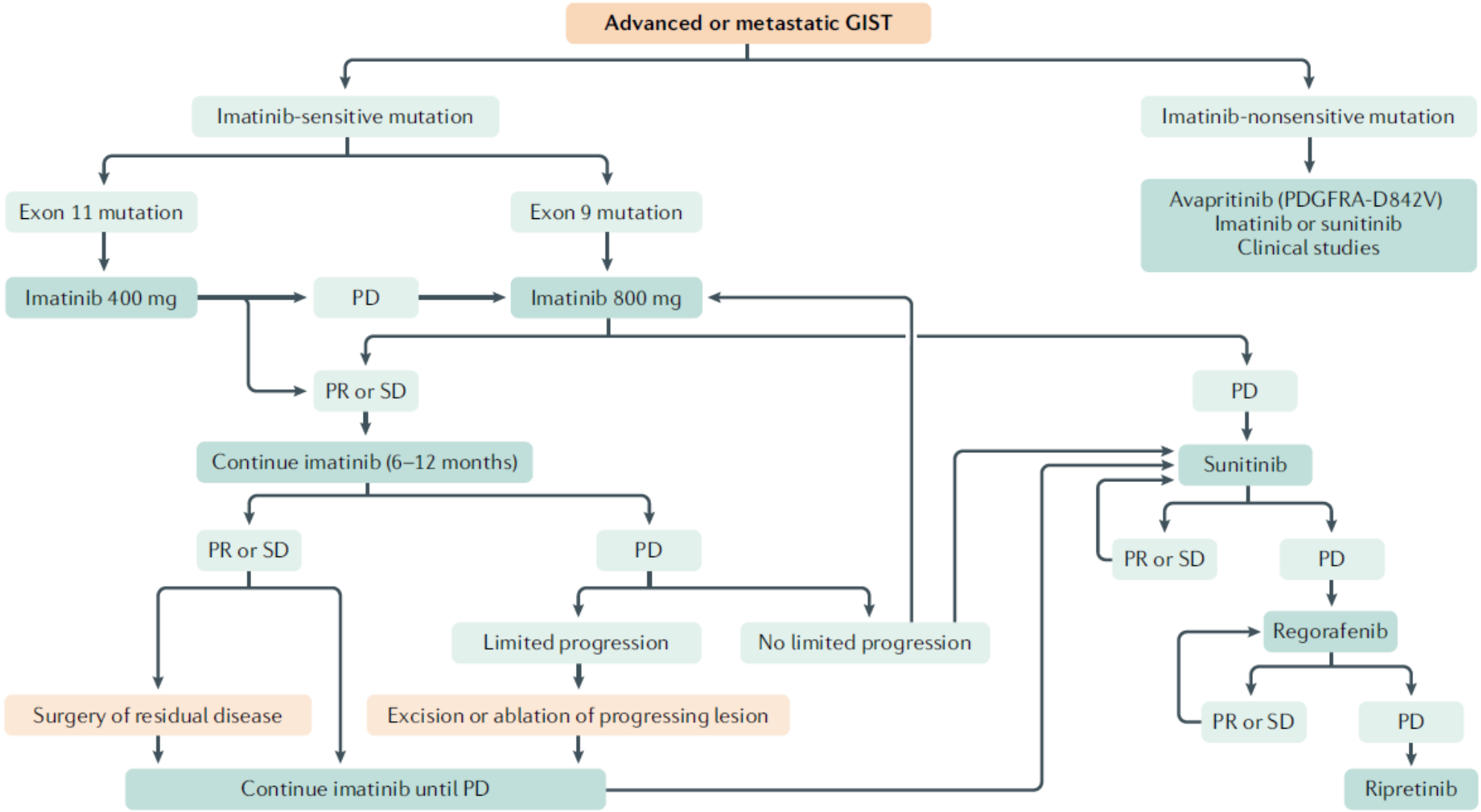
***Disclaimer**: I am not a physician. Nothing in this presentation should be regarded as medical advice or as a substitute for consulting with your doctors.*

Sub-types of GIST: The “pie chart” of GIST driver mutations; 2022 update

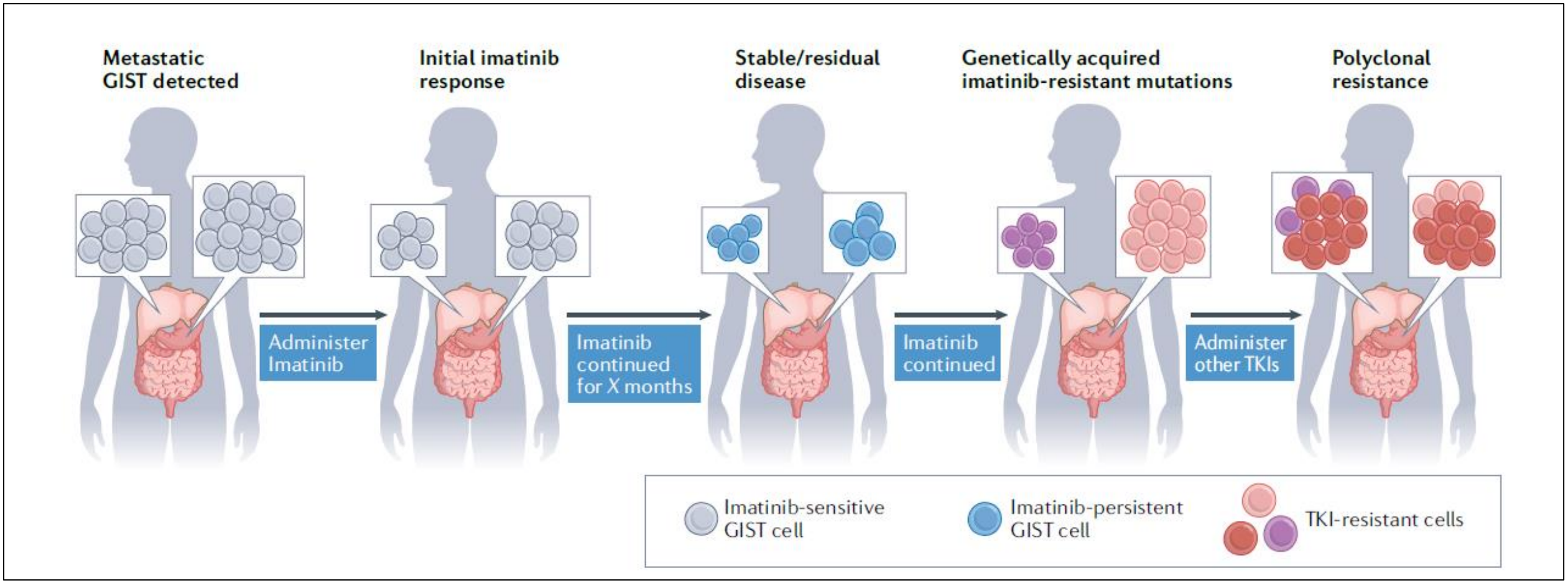


Klug *et al.*: Effective targeted therapies are now available for patients with GIST harbouring KIT and PDGFRA mutations, as well as those with BRAF mutations or receptor tyrosine kinase gene fusions. The remaining 12% of GISTs are SDH (succinate dehydrogenase) deficient, NF1, PIK3CA or RAS mutant, or otherwise “wild type”, and lack effective therapies (indicated by the grey segment of the outer ring).
Klug, Khosroyani, Kent, and Heinrich, New treatment strategies for advanced-stage GISTs, *Nature reviews: Clinical oncology* 19: 328-341, 2022.

Advanced GIST: treatment roadmap; Blay *et al.*, *Nature reviews. Disease primers*, 2021

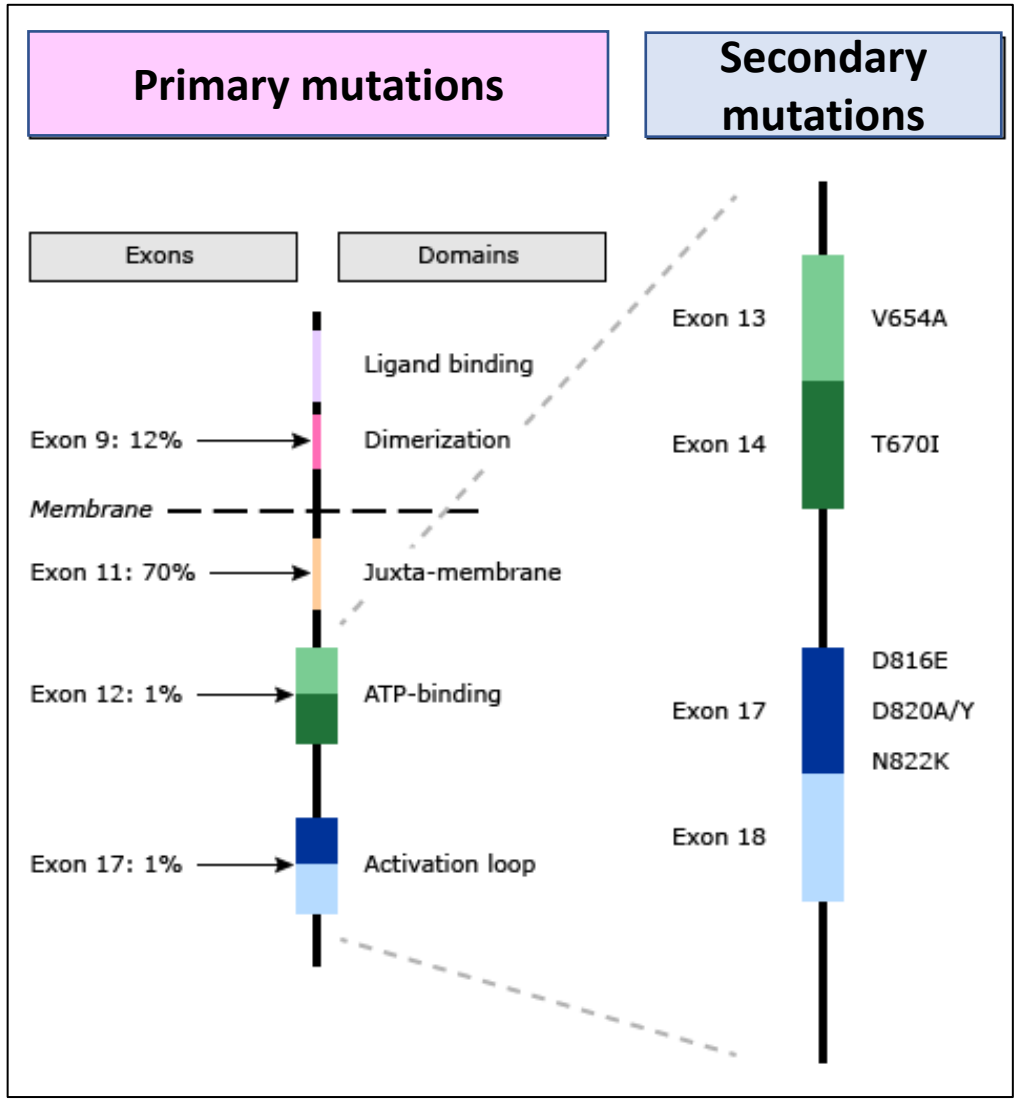


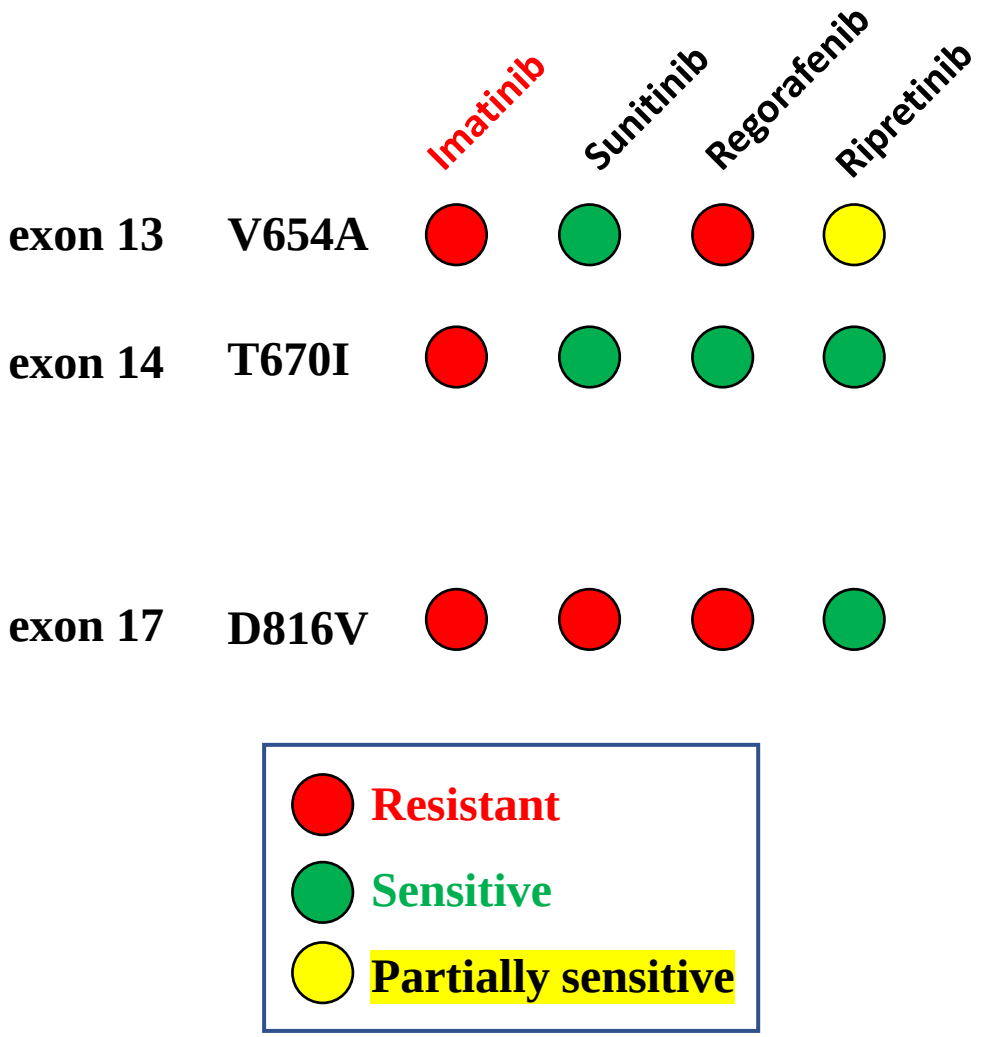
Klug *et al.*: Typical pattern of response and evolution during treatment of metastatic GIST



TKI = tyrosine kinase inhibitor (e.g. imatinib)

KIT secondary mutations (imatinib-resistant)





adapted from: Gramza … Heinrich, *Clin. Cancer Res.* 2009; Serrano and Fletcher, *Oncotarget* 2019

What strategies may be effective against (multiple) imatinib-resistant clones of GIST cells?

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

- **Combinations of TKIs**
  - **broader spectrum of activities, but what about side effects?**

- **Attacking the KIT signaling pathway further "downstream', *e.g.* MEK inhibitors**

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

- **Local treatments, e.g. surgery, radiofrequency ablation …**

All of these avenues are being explored.

Ripretinib update

Ripretinib was *not* superior to sunitinib in second line, but it has been approved for use in fourth line.

Ripretinib versus sunitinib in patients with advanced GIST after treatment with imatinib (INTRIGUE): a randomized, open-label, phase III trial, Bauer *et al.*, *J. Clin. Oncol.* 2022 (Aug 10)

We compared efficacy and safety of ripretinib versus sunitinib in patients with advanced GIST who were previously treated with imatinib (INTRIGUE, ClinicalTrials.gov identifier: NCT03673501).

***Results:* Median PFS for ripretinib and sunitinib was 8.0 and 8.3 months, respectively.**

Ripretinib was associated with a more favorable safety profile, fewer grade 3/4 treatment-emergent adverse events, and better scores on patient-reported outcome measures of tolerability.

***Conclusion:* Ripretinib was not superior to sunitinib in terms of PFS. However, meaningful clinical activity, fewer grade 3/4 treatment-emergent adverse events, and improved tolerability were observed with ripretinib.**

Ripretinib in Canada: update

In late 2021, LRG Canada submitted* patient-group input to CADTH, which was evaluating ripretinib (Qinlock™) for provincial funding in Canada.

Manufacturer: Medison Pharma Canada Inc. (for Deciphera)

CADTH's final recommendation was positive (April 28, 2022).

Pricing negotiations with the provinces are presumably still ongoing.

GIST: New KIT inhibitors: drug development / clinical trials update

Drug/ drug combination	Predicted efficacy	
	KIT-mutant GIST	*PDGFRA*-mutant GIST
THE-630	✓	×
NB003 (AZD3229)	✓	✓
IDRX-42	✓	✓
Bezuclastinib + sunitinib	✓	✓

(adapted from Klug *et al.*, 2022)

THE-603: Theseus Pharmaceuticals
NB003: (formerly AZD3229 – AstraZeneca): Ningbo Newbay Tech. Development Co.
IDRX-42: IDRx, Inc. (launched Aug. 2022); licensed from Blueprint
Bezuclastinib: (formerly PLX 9486 – Plexxikon – now shut down): Cogent Biosciences

THE-630 (Theseus Pharmaceuticals)

May 12, 2022

“In January 2022, the first patient was treated in a Phase 1/2 dose escalation and expansion clinical trial of THE-630 in patients with advanced GIST.

THE-630 is a single molecule pan-variant inhibitor of KIT, designed for patients whose cancer has developed resistance to earlier lines of therapy.

The Company continues activating sites and enrolling patients in this study, with initial data from the Phase 1 portion of the clinical trial expected to be presented at a scientific conference in the first half of 2023.”

(No trial sites in Canada yet.)

NB003 (Ningbo Newbay Tech. Development Co.)

Phase 1, Open-label, Multicenter Study to Assess the Safety, Tolerability, and Pharmacokinetics of NB003 in Subjects with Advanced Solid Tumors

This is a study of NB003 administered orally in patients with advanced GIST who have progressed on or had an intolerability to imatinib …

Recruiting at Memorial Sloan Kettering Cancer Center, NYC; Principal Investigator: Chi Ping

Also Beijing and Shanghai, China; no sites in Canada yet.

IDRX-42

From: Paul Lim, Blueprint Medicines
Sent: Tues. Aug. 2, 2022

I wanted to share with you the news that Blueprint Medicines has licensed a development candidate-stage KIT exon 13 inhibitor to IDRx, a clinical-stage biopharmaceutical company focused on purpose-built precision combination therapies in cancer.

First-in-human study of IDRX-42; Dana-Farber Cancer Institute, Boston; Contact: Suzanne George, MD

***Cancer Research* 82, Supplement, 15 June 2022; Poster Presentations - Late-Breaking Abstracts**
Abstract LB565: Efficacy of a highly potent and selective KIT V654A inhibitor for treatment of imatinib resistant GIST; Alexandra R. Grassian *et al.*

CTOS 2022: Anti-tumor effects of the novel Kit mutant inhibitor M4205/IDRX-42 in GIST xenograft models; Patrick Schöffski, Leuven Cancer Institute.

Bezuclastinib + sunitinib ("PEAK" trial; Cogent Biosciences)

Part 1a: patients receive bezuclastinib + sunitinib (dose escalation lead-in to determine the dose of a new bezuclastinib formulation that will be administered in Part 1b and Part 2).

Part 1b: patients are randomized 1:1 to receive either bezuclastinib or sunitinib as single agent for 2 weeks, followed by bezuclastinib + sunitinib.

Part 2: patients are randomized 1:1 to receive either bezuclastinib + sunitinib or sunitinib only.

***Crossover:* Patients in the sunitinib-only group who have blinded independent review confirmed disease progression on study will be permitted to crossover to receive bezuclastinib + sunitinib.**

From: Lora Marden, Cogent Biosciences; Sent: Fri. Oct. 22, 2022

"We are hoping to have the trial up and running in Canada in early 2023."

For more information: **cogentclinicaltrials.com/peak** **Email: peakinfo@cogentbio.com**

GIST Immuno-oncology (Klug et al., 2022)

"Immunotherapy approaches have impressive activity against advanced- stage tumours of certain histologies (such as melanoma, non-small-cell lung cancer and renal cell carcinoma). However, immune-checkpoint inhibitors … have thus far shown only modest activity in patients with GIST. …

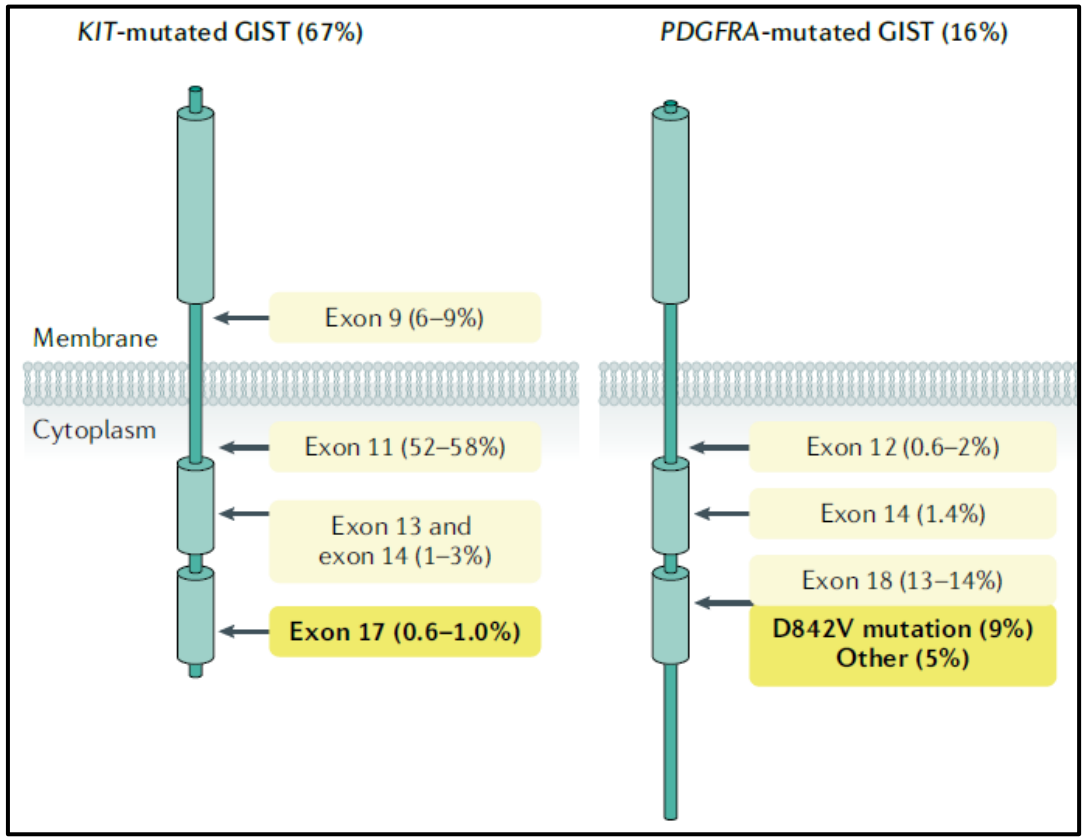
Similar to these clinical findings, monotherapy with anti-PD-1 or anti-PD-L1 antibodies had no effect on tumour growth in a mouse model of GIST; however, addition of an anti-PD-1 antibody to imatinib markedly decreased tumour growth compared with single-agent imatinib. Thus, the feasibility of combining TKIs with immunostimulatory agents needs to be tested in clinical studies."

PD-1: a checkpoint protein on T cells (immune cells). PD-1 helps keep T cells from attacking normal cells in the body, via binding to PD-L1 protein on some normal (and cancer) cells. Some cancer cells express PD-L1, which helps them "hide" from immune attack.

Mutational testing in Canada

LRGC is continuing its efforts to improve access to mutational testing for all Canadian GIST patients. Our goal is universal access. We are close to this goal in many provinces, but still short of it in some provinces and regions. Both *jurisdictional/administrative obstacles* and *lack of physician awareness* contribute to the problem.

PDGFRA-mutant GIST



Blay *et al., Nature reviews. Disease primers,* 2021

***PDGFRA*:**

Among *PDGFRA*-mutant GISTs, the substitution D842V (aspartic acid → valine) is much the most common.

This variant is imatinib-resistant.

Avapritinib is the drug of choice.

However, as Mike Heinrich noted at LifeFest, PDGFRA mutations other than D842V are sometimes found (including other substitutions at position 842). Some of these variants are imatinib *sensitive*.

Message: *Not all PDGFRA-mutant GISTs are the same*.

Cell-free DNA in human blood:

Mandel, P. and Metais, P. Les acides nucléiques du plasma sanguin chez l'homme, *Comptes rendus des seances de la Soc de biologie et de ses filiales* 142, 241-243 (1948).

www.youtube.com/watch?v=3S820qcnUmI

A cautious view: "ctDNA mutations … were only detectable in those with advanced disease after imatinib failure … Given low ctDNA shedding, the use of this technology to aid in decision-making remains non-standard, and prospective studies on the use of personalizing therapy based upon ctDNA observed secondary mutations … are lacking."

Senchak, Ahr, and von Mehren, GISTs: What is the best sequence of TKIs?, *Curr. Treat. Options in Oncol.* (March 2022)

Prognostic impact of circulating tumor DNA detection in first-line treatment of advanced GIST
Kjetil Boye, Oslo University Hospital

ctos®

2022 Annual Meeting

November 16 - 19, 2022

Vancouver Convention Centre
Vancouver, BC, Canada

Session 7: GIST & Other Sarcomas with Actionable Targets

Friday, November 18, 2022 10:30 AM – 12:00 PM

Moderator(s)

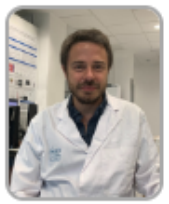
PC

Ping Chi, MD, PhD

Memorial Sloan Kettering Cancer Center
New York, New York, United States

Armelle Dufresne, N/A, MD PhD

Medical Oncologist
Medical Cancer Department, Centre Léon Bérard
Lyon, Auvergne, France



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