



Current and Emerging Medications for GIST

November 26, 2019

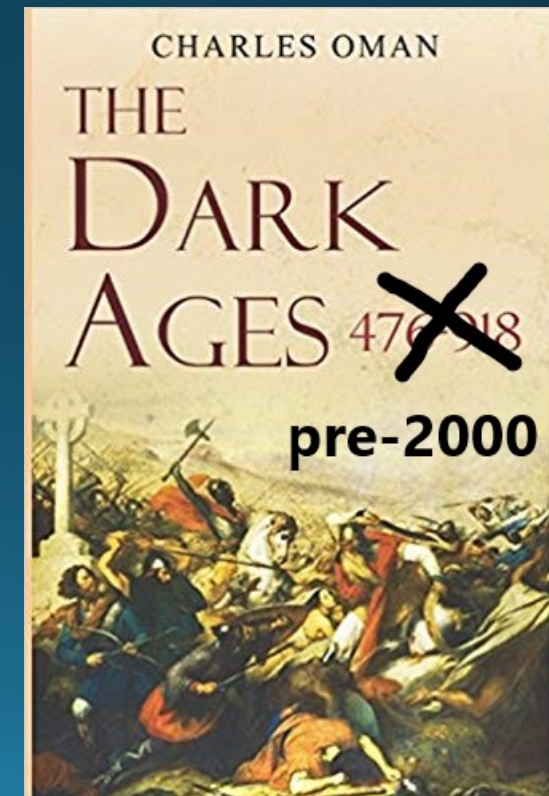
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Presentation Overview

- History – the pre-medication era
- Currently approved “general” medications (the first generation)
- New and emerging medications (the next generation)
- Impact on treatment of GIST

But First, a Bit of History...

- In the era prior to the development of the first generation of treatments for GIST, the only available medication for patients was traditional chemotherapy, which had a *high failure rate*.
- GIST patients were often misdiagnosed as having other cancers such as *Leiomyosarcoma (LMS)* – this is one reason why the misdiagnosed field exists in our Patient Registry.



Enter...The First Generation of GIST Drugs aka “The Original Series”

- These drugs were developed with *other diseases* in mind, and GIST came “along for the ride”
- They were more specifically targeted than traditional chemotherapy drugs, but only at the base mutation level (i.e. KIT) and not at the exon or mutation level (i.e. Exon 11, V600E)



Gleevec (Imatinib)

Manufacturer:	Novartis
Original Indication/Line:	CML and GIST; First Line
Dosage:	100 or 400 mg tablets (400 mg is common starting dose, patients can escalate to 800 mg and beyond), Continuous dosage
Approval Year:	2001
Status:	Generic (as of Feb 2016)
Targets:	Primarily KIT, PDGFR, also downstream pathways RAS/MapK, PI3K, JAK/STAT
Side Effects of Note:	Edema, eye bleeds, thinning of skin, fatigue, diarrhea, muscle cramps, anemia, bone deformation



Sutent (Sunitinib)

Manufacturer:	Pfizer
Original Indication/Line:	RCC and GIST; 2 nd line
Dosage:	12.5, 25 mg and 50 mg tablets (typical doses vary from 12.5 to 50 mg), can be continuous or cycled (4 weeks on/2 weeks off)
Approval Year:	2006
Status:	Name brand (not generic)
Targets:	KIT, PDGFR, VEGFR
Side Effects of Note:	Nausea, fatigue, skin issues (incl. HFS), skin/hair color changes, hypertension, liver and heart toxicity (rarer)



Stivarga (Regorafenib)

Manufacturer:	Bayer
Original Indication/Line:	Colorectal cancer (metastatic), Hepatocellular carcinoma, GIST; 3 rd line
Dosage:	40 mg tablets, typical max dose 160 mg (typically cycled 21 days on/7 days off)
Approval Year:	2013
Status:	Name brand (not generic)
Targets:	KIT, PDGFRA, VEGFR
Side Effects of Note:	Hand and foot syndrome, hypertension, diarrhea, liver toxicity (rarer)



These drugs were successful, but didn't help *all* GIST patients.

- They were not targeted to the exon or specific mutation level, so *some patients had non-responsive mutations and thus didn't benefit.*
- What was needed were *more specifically targeted drugs* that were designed for GIST patients from the beginning.

Presenting...The Next Generation of GIST Drugs

- These are more targeted, down to the specific mutation.
- In all cases, they were developed with GIST patients in the original trial.
- While the targeted audience is smaller due to specificity, the efficacy is also greater.
- One is currently approved, and three more are currently in trial and expected to be approved shortly.
- Full Disclosure: LRG has recently been in contact with all of these companies.



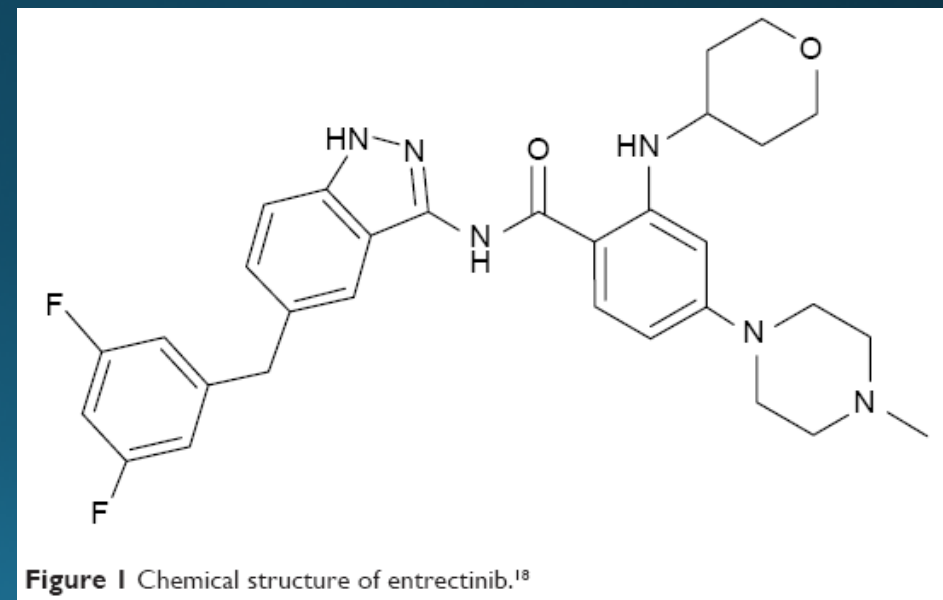
Vitrakvi (Larotrectinib)

Manufacturer:	Bayer/LOXO (Eli Lilly)
Original Indication/Line:	Various, including GIST; patients with a documented NTRK fusion Drug showed great efficacy and durable response in trial; 3 GIST patients (out of 55) in trial with 100% response rate.
Dosage:	25 or 100 mg tablets, oral suspension; 200 mg/day
Approval Year:	2018
Status:	Name brand (not generic)
Targets:	Various NTRK fusion partners (for GIST, relevant partner is NTRK3/ETV6)
Side Effects of Note:	Generally well tolerated; fatigue, nausea, dizziness, anemia



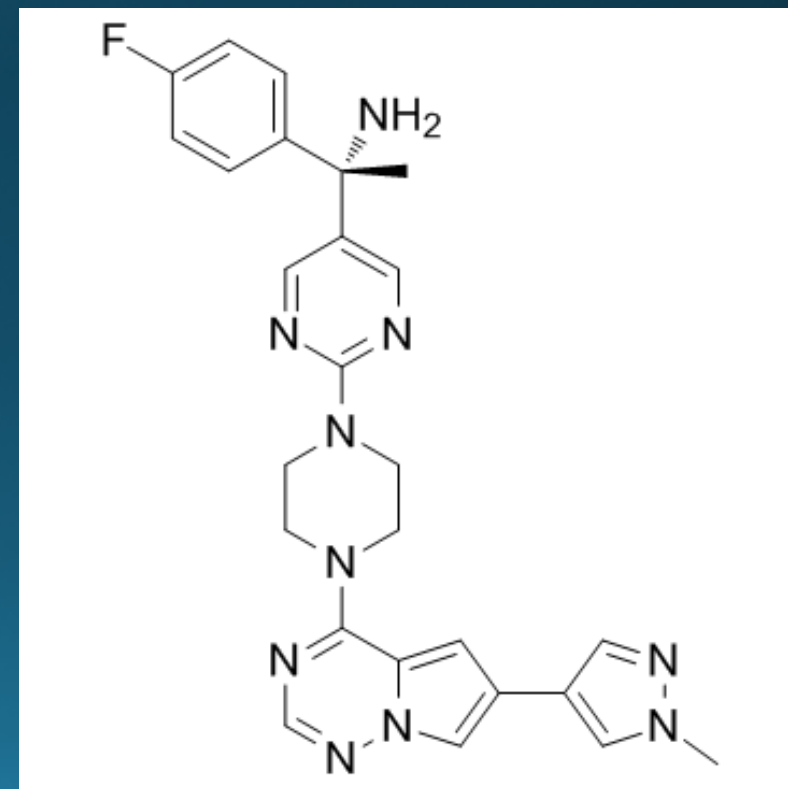
Entrectinib

Manufacturer:	Ignyta/Genentech/Roche
Original Indication/Line:	Various, including GIST; patients with a documented NTRK fusion
Dosage:	600 mg/daily
Approval Year:	2019
Status:	Name brand (not generic)
Targets:	Various NTRK fusion partners (for GIST, relevant partner is NTRK3/ETV6), ALK rearrangement
Side Effects of Note:	Generally well tolerated; fatigue, dizziness, weight increase, nausea, constipation, diarrhea



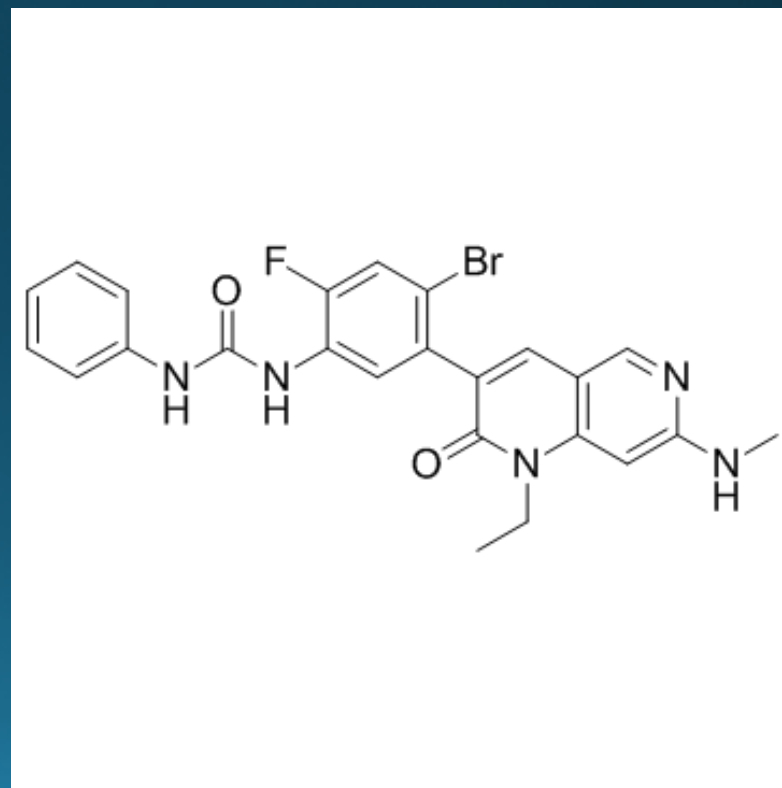
Avapritinib (BLU-285)

Manufacturer:	Blueprint Medicines
Original Indication/Line:	Mastocytosis and GIST; 1 st line for PDGFRA Exon 18 D842V, other lines pending (4 th , potentially 2 nd or 3 rd line)
Dosage:	Trial tested levels from 30 to 600 mg daily
Approval Year:	N/A (expectation is late 2019 or early 2020)
Status:	Currently in trial (as of November 2019) (167 KIT patients, 56 D842V)
Targets:	D842V (1 st line), KIT and PDGFRA GIST (later lines)
Side Effects of Note:	Nausea, fatigue, anemia, edema, diarrhea Memory impairment has been highlighted, appears to be dose-dependent and reversible



Ripretinib (DCC-2618)

Manufacturer:	Deciphera
Original Indication/Line:	Mastocytosis, gliomas, solid tumors, GIST; currently in trial for 2 nd , 3 rd , and 4 th line for GIST
Dosage:	150 mg daily
Approval Year:	N/A (expectation is 2020)
Status:	Currently in trial (as of November 2019) 2 nd line (INTRIGUE – n=38), 3 rd line (n=29), 4 th line (INVICTUS – n=111)
Targets:	KIT Exon 9, 11, 13, 17, PDGFRA Exon 14, 18 (incl. D842V)
Side Effects of Note:	Alopecia, muscle pain, fatigue, hand-foot syndrome

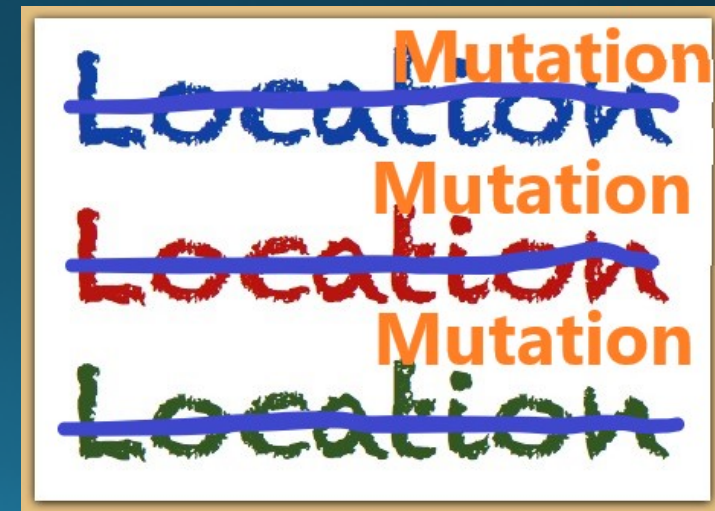


What does this mean for GIST patients?

"It is an interesting time to be a GIST patient"

Sebastian Bauer, CTOS 2018

- A number of promising treatments are on the horizon. It is quite possible that we can go from 5 approved treatments today to as many as 7 by the end of 2020.
- All of these new treatments are more specifically targeted than those of the previous generation.
- Now more than ever – **MUTATIONAL TESTING IS KEY!**



Questions?

