Gastrointestinal Stromal Tumor (GIST) Treatment Landscape In 2022

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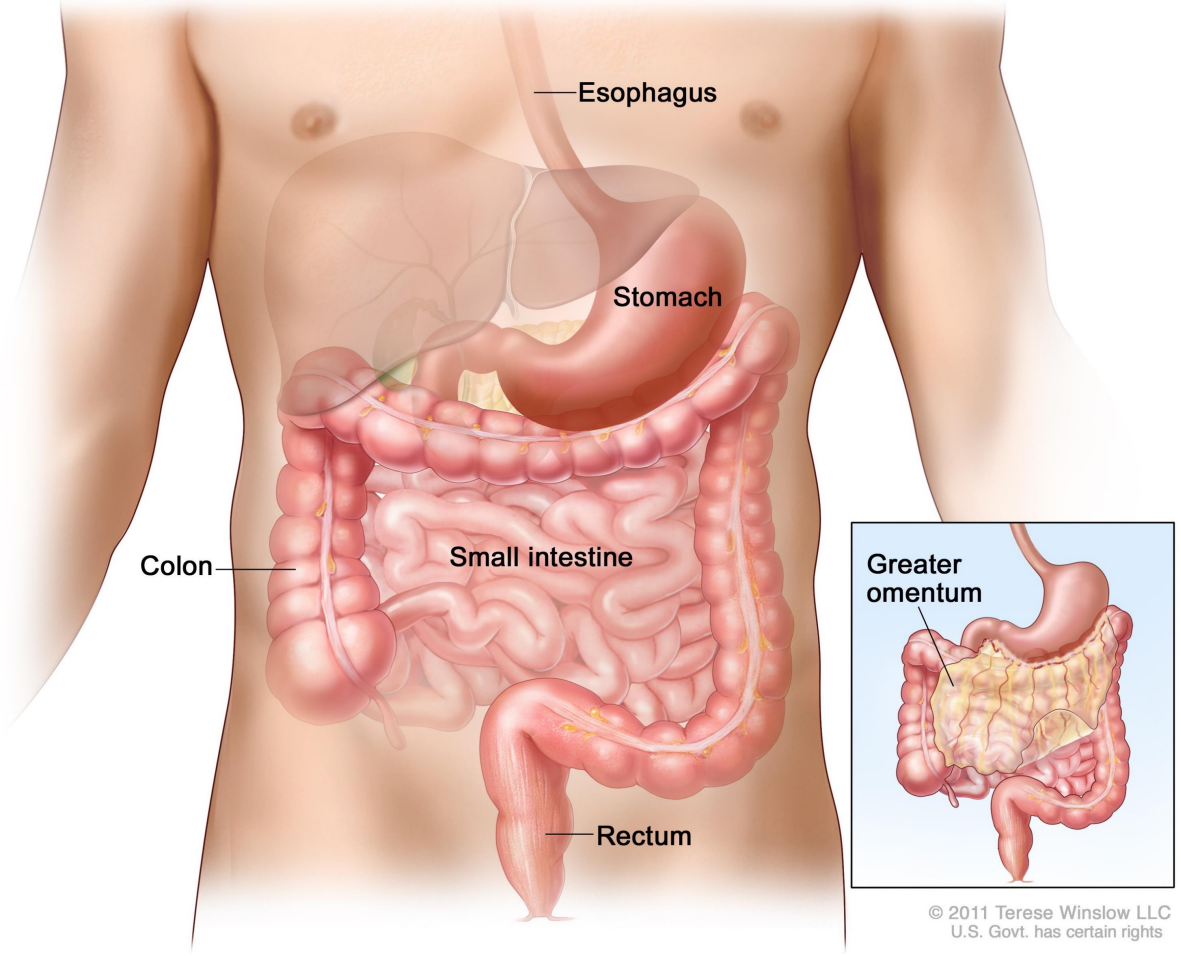
Outline

- Treatment PRIOR to 2020 (BC- before COVID)
  - Curable
  - Treatable

- Updates in GIST what's happening in the 2020s AC (after COVID)
  - Newly FDA treatments
  - Updates in NCCN guidelines
  - Phase 3 clinical trials

WHERE DOES GIST START?



- Stomach (60%).
- Small intestine (30%).
- Rectum (3%).
- Colon (1–2%).
- Esophagus (<1%).
- Omentum/mesentery (rare).

Back to the Basics: Cancer and GIST 101

- Curable: treatment that you receive can eliminate the cancer from your body and it never comes back
  - Surgery is the cure
  - Must be done by experience surgeon in GIST
- High risk
  - Curable but high likelihood of recurrence
  - additional therapy can be given to prevent if from recurring
    - Adjuvant- treatment given *after* the cure (surgery)
    - *Neo*adjuvant- treatment given *before* the cure (surgery)

- Treatable:
  - Metastatic/multifocal/unresectable/recurrent-Can't eliminate the cancer totally from body but can control it, protect organs and you can live with it
  - First line, second line, third line- terms for treatments in the metastatic setting

Updates in Curable GIST

- Surgery still the standard- MUST be done by GIST/sarcoma surgeon
- Now upfront imatinib given neoadjuvant is recommended if unresectable, borderline resectable to resection can cause too much harm
- Every tumor should be sent for molecular testing

Table 1. Guidelines for Risk Assessment of Primary Gastrointestinal Stromal Tumor (GIST)

Tumor Parameters		Risk of Progressive Disease# (%)			
Mitotic Rate	*Size*	*Gastric*	*Duodenum*	*Jejunum/Ileum*	*Rectum*
≤5 per 50 high-power fields (HPF)	≤2 cm	None (0%)	None (0%)	None (0%)	None (0%)
	>2 - ≤5 cm	Very low (1.9%)	Low (8.3%)	Low (4.3%)	Low (8.5%)
	>5 - ≤10 cm	Low (3.6%)	(Insufficient data)	Moderate (24%)	(Insufficient data)
	>10 cm	Moderate (10%)	High (34%)	High (52%)	High (57%)
>5 per 50 HPF	≤2 cm	None##	(Insufficient data)	High##	High (54%)
	>2 - ≤5 cm	Moderate (16%)	High (50%)	High (73%)	High (52%)
	>5 - ≤10 cm	High (55%)	(Insufficient data)	High (85%)	(Insufficient data)
	>10 cm	High (86%)	High (86%)	High (90%)	High (71%)

Defined as metastasis or tumor-related death.
Denotes small number of cases.

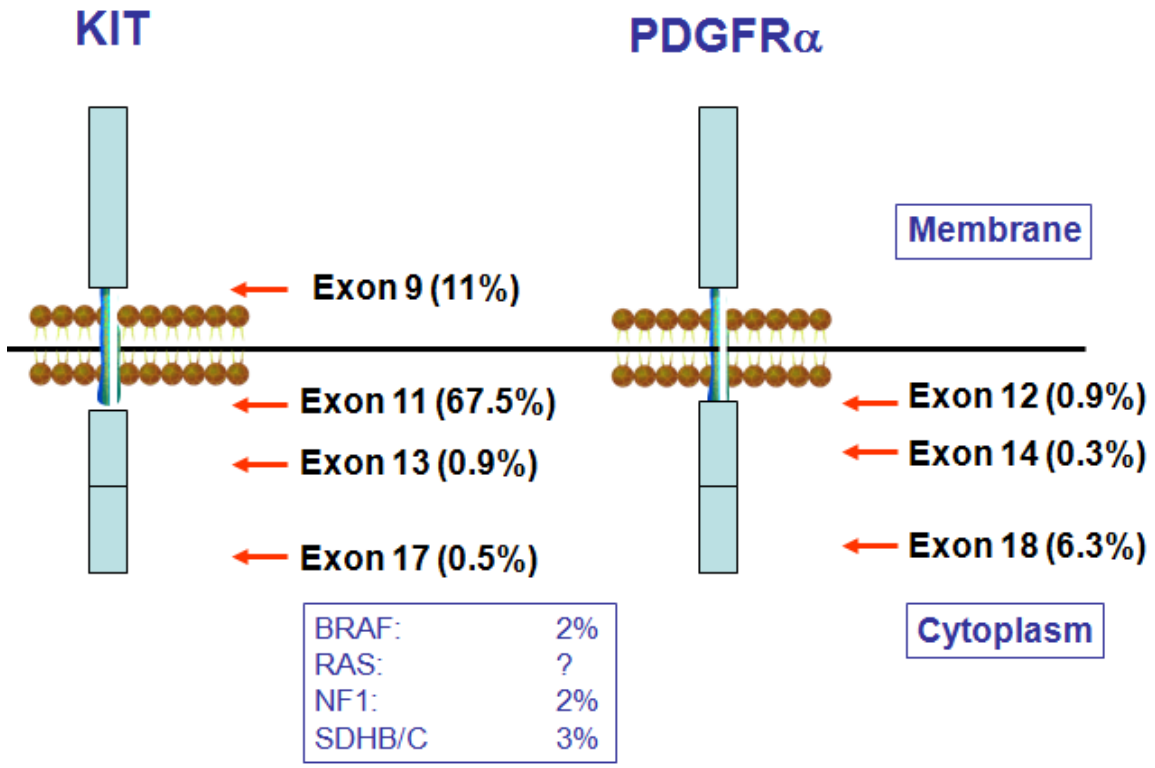
3 MAIN factors to determine risk of recurrence:

1. **Size** of tumor
2. **Primary Location** of the primary tumor
3. **Mitotic index** of the tumor

Updates in Adjuvant Treatment

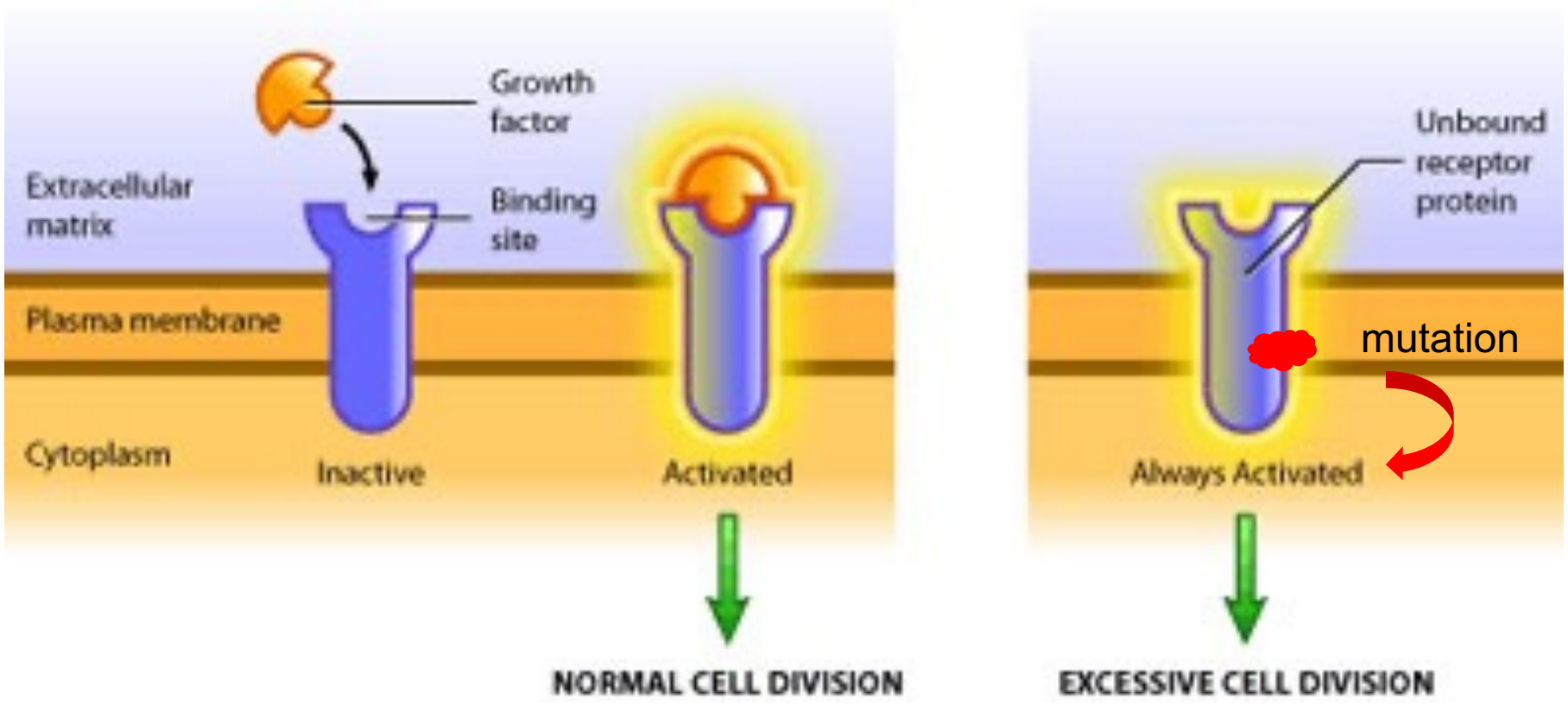
- MUST test for mutation status to make sure treatment will help
- Imatinib at 400 mg daily ONLY FDA approved dose
- Imatinib at 800 mg (400mg twice per day) now offered to patients if Exon 9 mutations
- ?? Should you receive Avapritinib for high risk D842V GIST???

Mutations in KIT in GIST



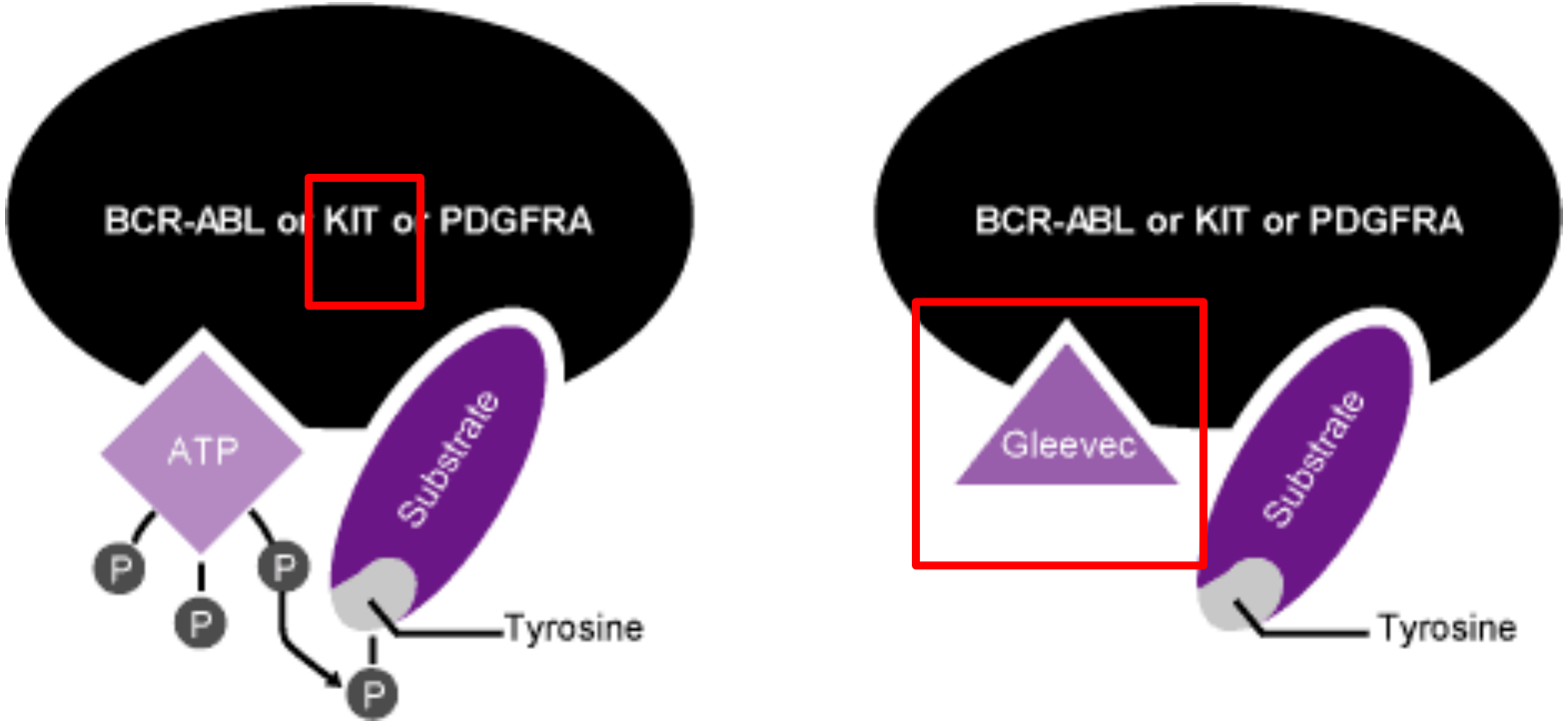
There are several **different areas** in several **different genes** that can cause GIST and based on the gene and location in the gene will help determine best treatment

WHAT DOES IT MEAN TO HAVE A MUTATION?



Mutations code for **proteins**

These mutations in genes that code for proteins responsible to cell growth can cause the cell to grown and divide


BCR-ABL or KIT or PDGFRA
ATP
P
P
P
P
Substrate
Tyrosine
BCR-ABL or KIT or PDGFRA
Gleevec
Substrate
Tyrosine

Quick Recap of Pre-COVID FDA approved Treatments for GIST

IN PURSUIT OF *YOUR CURE.*™

Generic name	Brand Name	Receptor Targets	FDA Approval	Trial that led to Approval	Effective mutations
Imatinib	Gleevec	Type II kinase inhibitor ABL, **KIT**, **PDGFRa**	2002-1st line metastatic GIST 2008- adjuvant for 1 year 2012-adjuvant for 3 years	Phase 2- 80% clinical benefit rate Phase 3-Z9001 trial 97% vs 83% RFS placebo Phase 3-SGGXVIII trial improved OS 3 v 1 years	Exon 11, 9 (needs higher dose), PDGRa
Sunitinib	Sutent	Type II kinase inhibitor VEGFR 1, 2, FLT3, **KIT**, **PDGFR a**,b	2006- 2nd line metastatic GIST	Phase 3 trial mPFS 6.3 mos. vs 1.5 mos. placebo	Exon 9, 11, 13
Regorafenib	Stivarga	Type II kinase inhibitor VEGFR 1, 2 RET, **KIT**, **PDGFR-a**, RET, BRAF, FGFR1	2013-3rd line metastatic GIST	GRID phase 3 trial 4.8 mos vs .9 mos placebo	Exon 11, 17, 9

POST- COVID treatment options

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR UNRESECTABLE,[c] PROGRESSIVE OR METASTATIC DISEASE

First-line therapy	Second-line therapy	Third-line therapy	Fourth-line therapy	Additional options after progression on approved therapies[d,e]
Preferred Regimen • Imatinib[f,1,2] (category 1) for sensitive mutations or for *PDGFRA* exon 18 mutations (excluding the D842V mutation)	Preferred Regimen • Sunitinib[f,6] (category 1) • Dasatinib[f] for patients with *PDGFRA* exon 18 mutations that are insensitive to imatinib (including the PDGFRA D842V mutation)	Preferred Regimen • Regorafenib[f,8] (category 1)	Preferred Regimen • Ripretinib 150 mg daily[f,9] (category 1)	Useful in Certain Circumstances • Avapritinib[f,3] • Cabozantinib[10] • Everolimus + TKI[g,11] • Nilotinib[12,13] • Pazopanib[14] • Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)[f,h,15] • Sorafenib[16-18]
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Useful in Certain Circumstances • *NTRK* gene-fusion positive GISTs only ‣ Larotrectinib[4] ‣ Entrectinib[5]				

Treatment Landscape Change from 2014-2022

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR UNRESECTABLE,[c] PROGRESSIVE OR METASTATIC DISEASE

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NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Soft Tissue Sarcoma

GIST[h]
- Imatinib[21,22]
- Sunitinib[23]
- Regorafenib[24]

Disease progression after imatinib, sunitinib, and regorafenib
- Sorafenib[25-27]
- Nilotinib[28,29]
- Dasatinib[30] (for patients with D842V mutation)

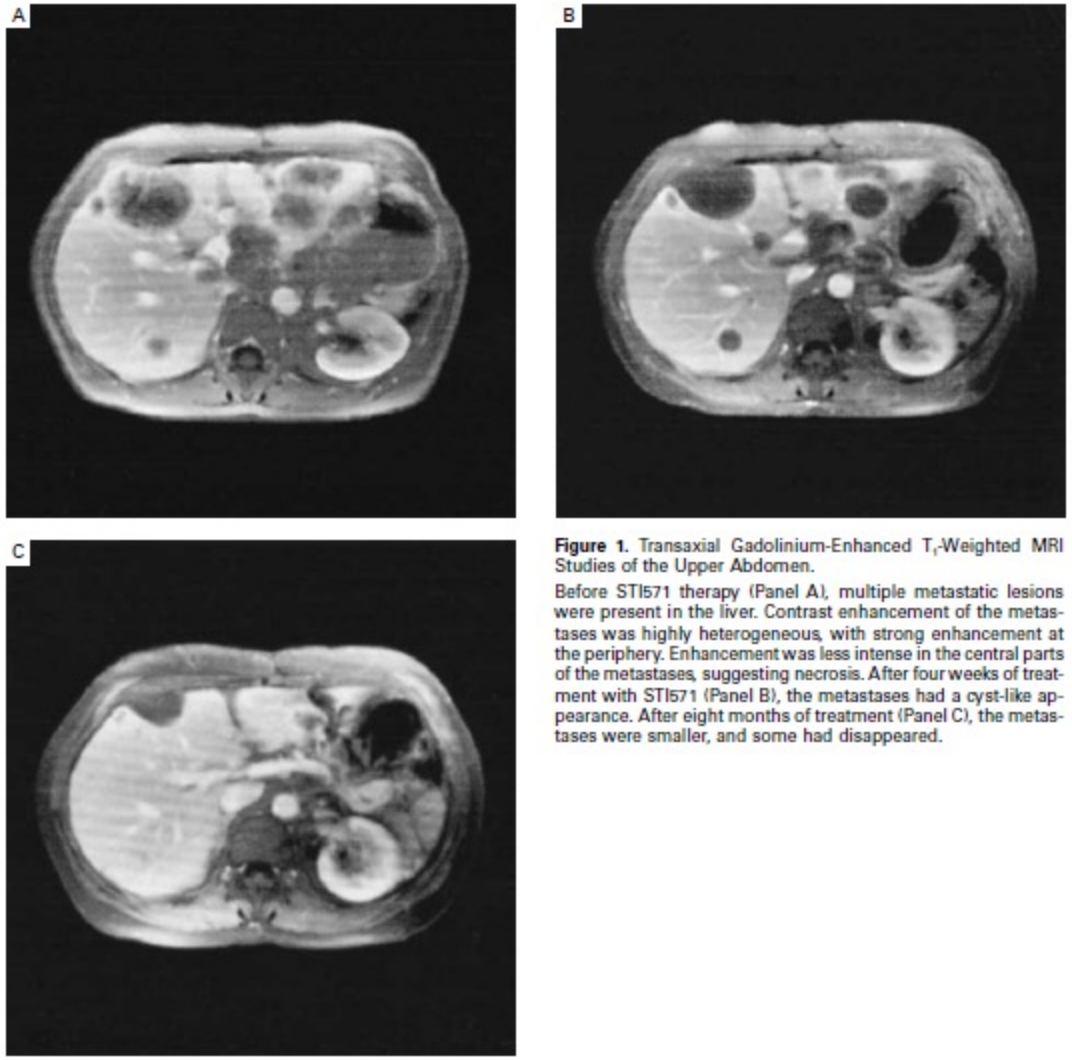


Figure 1. Transaxial Gadolinium-Enhanced T_1-Weighted MRI Studies of the Upper Abdomen.

Before STI571 therapy (Panel A), multiple metastatic lesions were present in the liver. Contrast enhancement of the metastases was highly heterogeneous, with strong enhancement at the periphery. Enhancement was less intense in the central parts of the metastases, suggesting necrosis. After four weeks of treatment with STI571 (Panel B), the metastases had a cyst-like appearance. After eight months of treatment (Panel C), the metastases were smaller, and some had disappeared.

Effect of the Tyrosine Kinase Inhibitor STI571 in a Patient with a Metastatic Gastrointestinal Stromal Tumor

Heikki Joensuu, M.D., Peter J. Roberts, M.D., Maarit Sarlomo-Rikala, M.D., Leif C. Andersson, M.D., Pekka Tervahartiala, M.D., David Tuveson, M.D., Ph.D., Sandra L. Silberman, M.D., Ph.D., Renaud Capdeville, M.D., Sasa Dimitrijevic, Ph.D., Brian Druker, M.D., and George D. Demetri, M.D.

The New England Journal of Medicine

EFFICACY AND SAFETY OF IMATINIB MESYLATE IN ADVANCED GASTROINTESTINAL STROMAL TUMORS

GEORGE D. DEMETRI, M.D., MARGARET VON MEHREN, M.D., CHARLES D. BLANKE, M.D., ANNICK D. VAN DEN ABBEELE, M.D., BURTON EISENBERG, M.D., PETER J. ROBERTS, M.D., MICHAEL C. HEINRICH, M.D., DAVID A. TUVESON, M.D., PH.D., SAMUEL SINGER, M.D., MILOS JANICEK, M.D., PH.D., JONATHAN A. FLETCHER, M.D., STUART G. SILVERMAN, M.D., SANDRA L. SILBERMAN, M.D., PH.D., RENAUD CAPDEVILLE, M.D., BEATE KIESE, M.SC., BIN PENG, M.D., PH.D., SASA DIMITRIJEVIC, PH.D., BRIAN J. DRUKER, M.D., CHRISTOPHER CORLESS, M.D., CHRISTOPHER D.M. FLETCHER, M.D., AND HEIKKI JOENSUU, M.D.

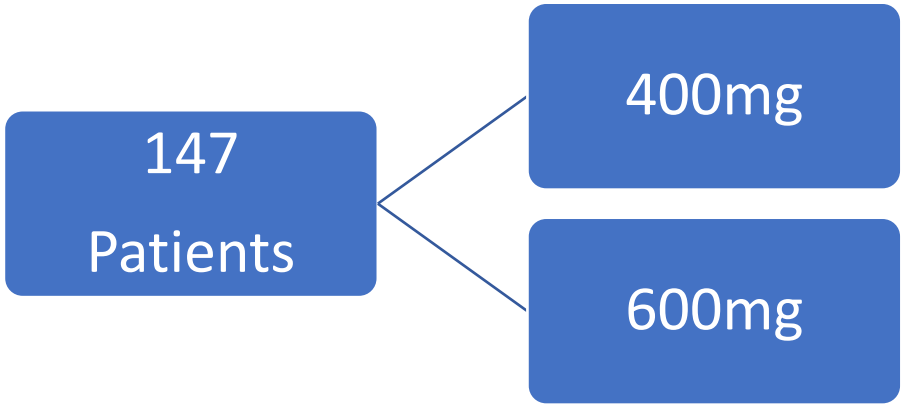


TABLE 2. RESPONSES TO IMATINIB IN PATIENTS WITH ADVANCED GASTROINTESTINAL STROMAL TUMORS.*

BEST RESPONSE	400 mg (N=73)	600 mg (N=74)	EITHER DOSE (N=147)
		no. (% [95% CI])	
Complete response	0	0	0
Partial response	36 (49.3 [37.4–61.3])	43 (58.1 [46.1–69.5])	79 (53.7 [45.3–62.0])
Stable disease	23 (31.5 [21.1–43.4])	18 (24.3 [15.1–35.7])	41 (27.9 [20.8–35.9])
Progressive disease	12 (16.4)	8 (10.8)	20 (13.6)
Could not be evaluated	2 (2.7)	5 (6.8)	7 (4.8)

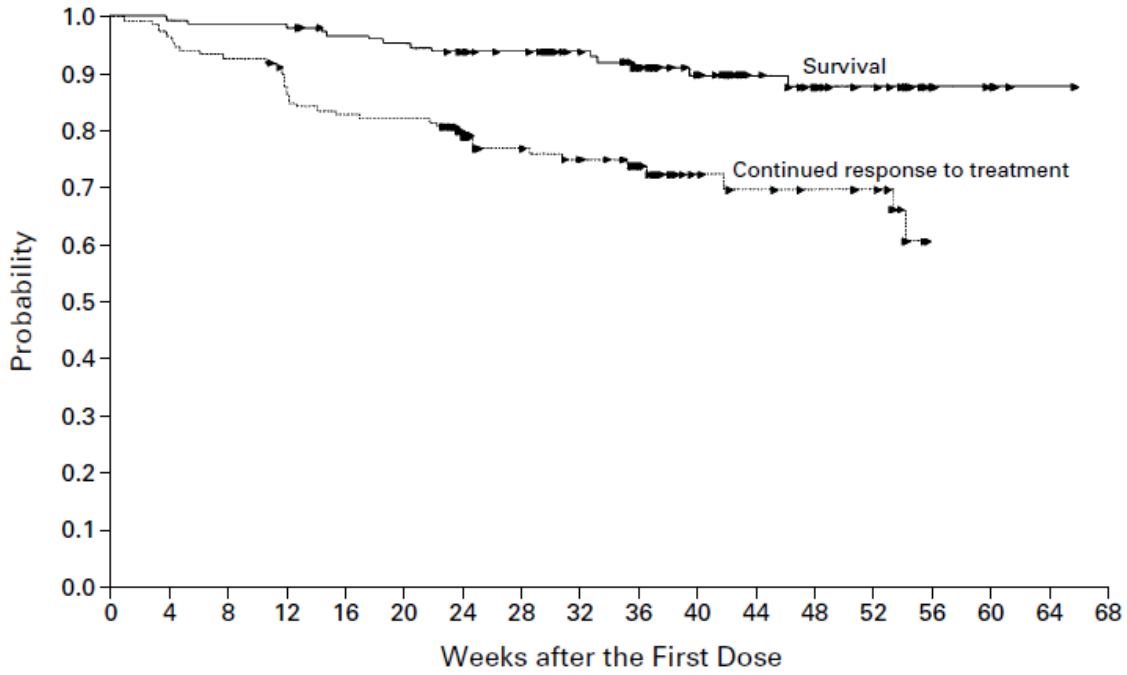
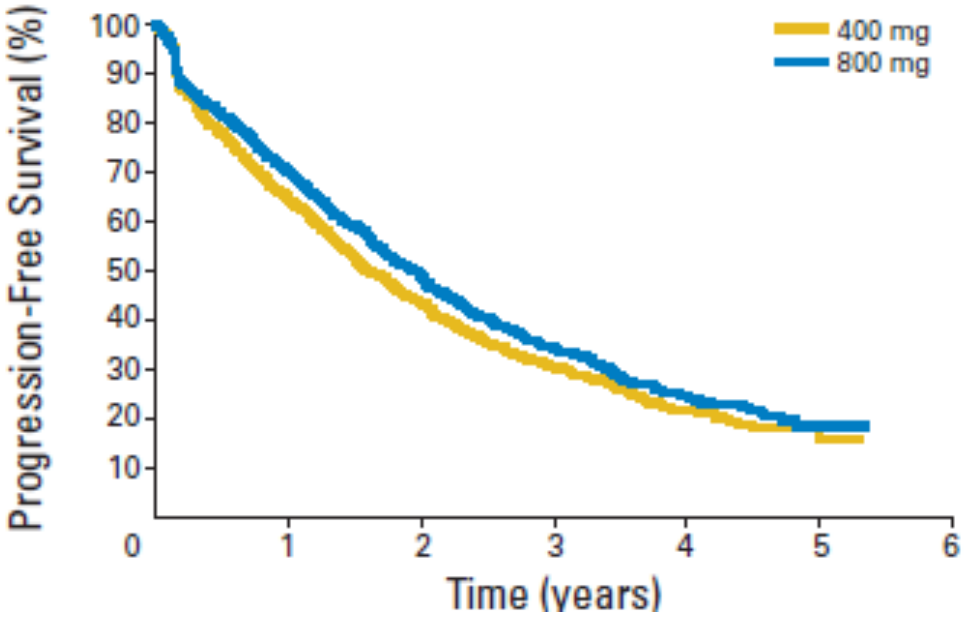


Figure 1. Kaplan–Meier Estimates of Overall Survival and Time to Treatment Failure for All Patients. Each arrowhead represents the point at which a patient's data were censored.

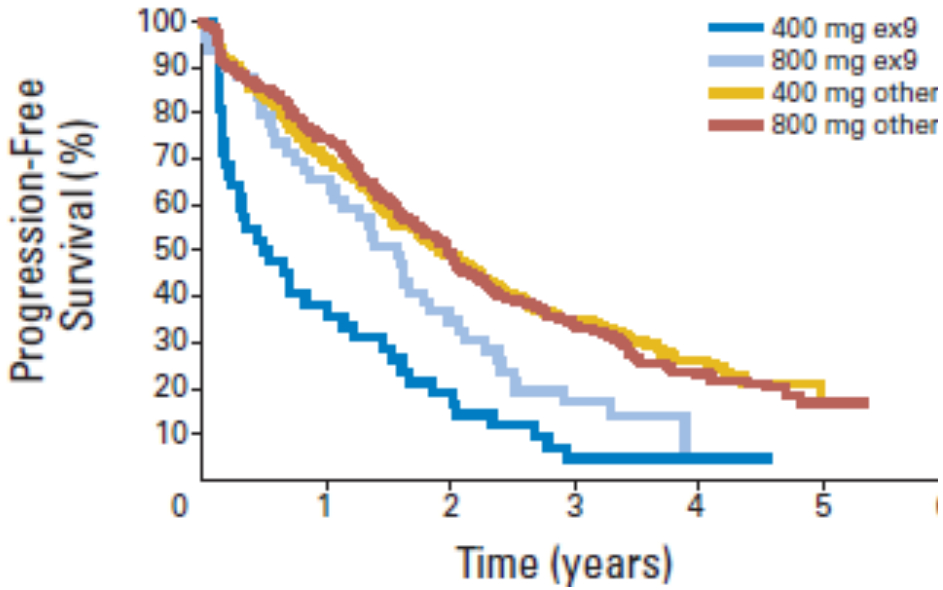
What is the right dose of Gleevec?

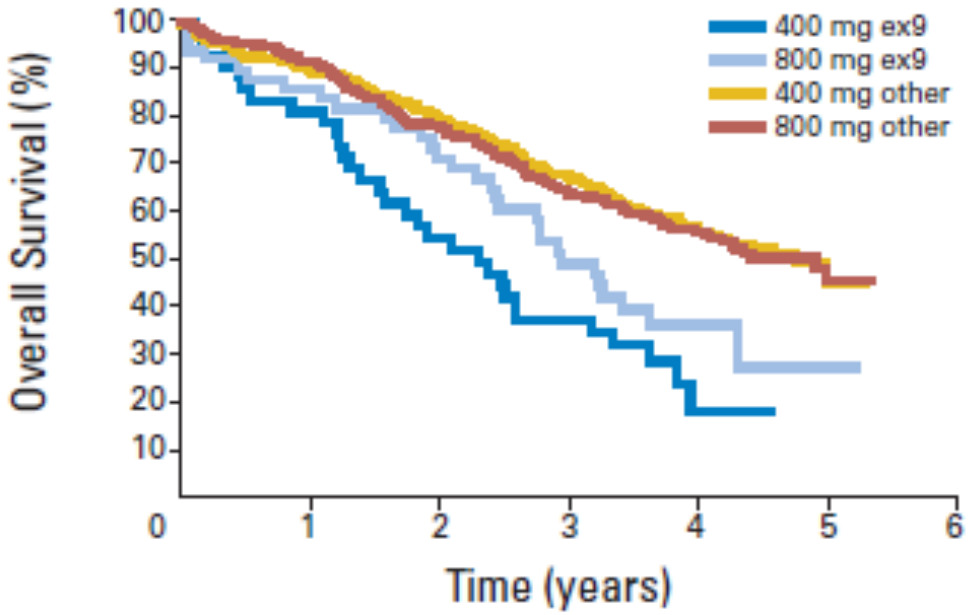


- 1640 pts with advanced GIST

J Clin Oncol 28:1247-1253.

Response by Mutational Status





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Response by Genotype

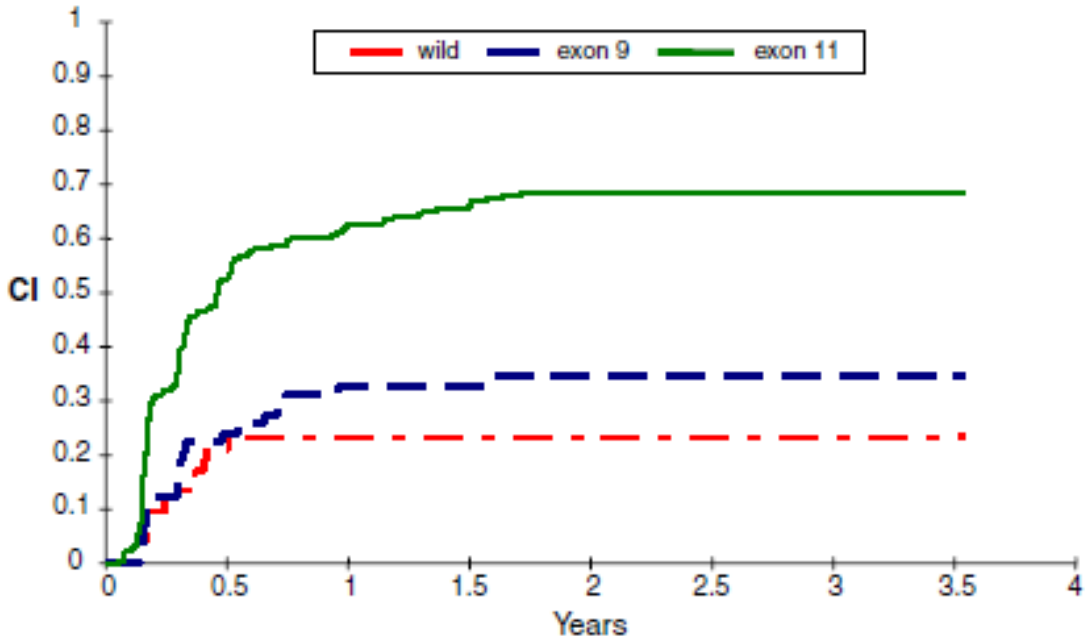
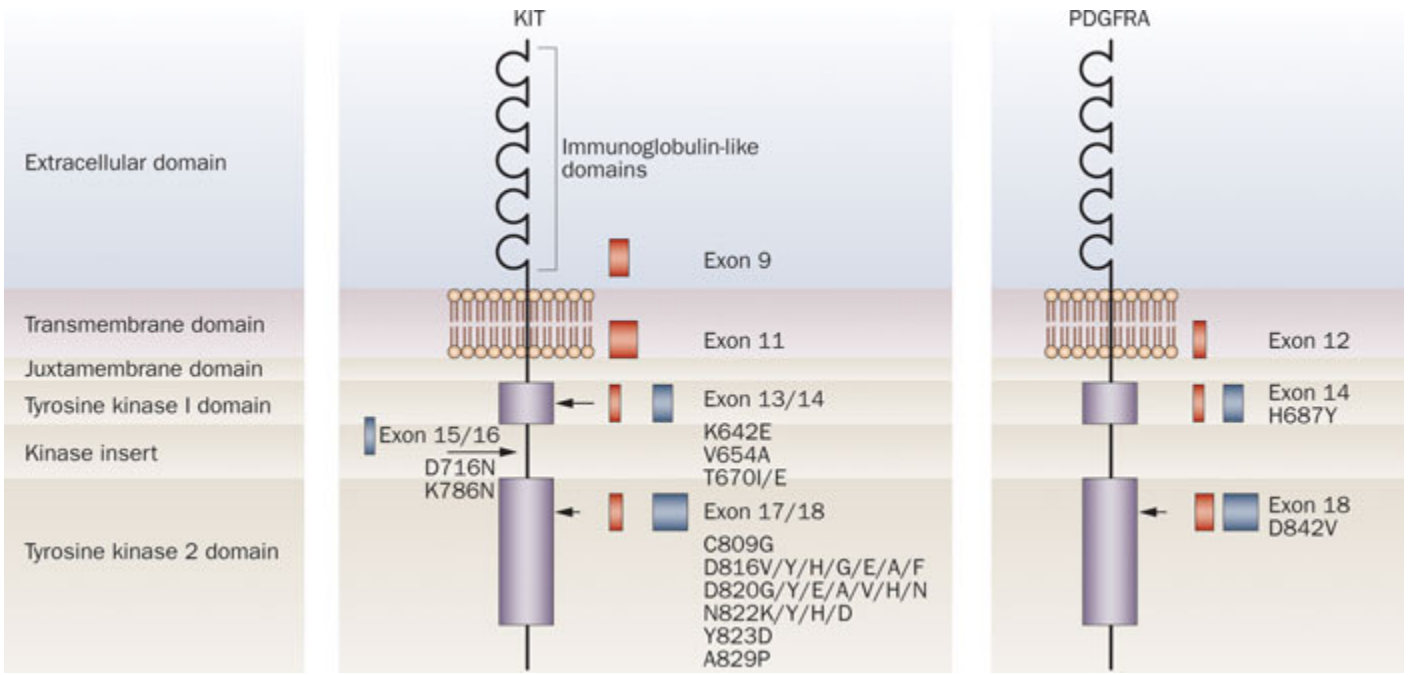


Fig. 3 – Cumulative incidence of response observed in the three largest subgroups of kinase genotypes analyzed in this study.

Resistance to Imatinib

- 5% primary resistance
- 14% have early resistance
- Secondary /acquired resistance
  - Median of 2 years

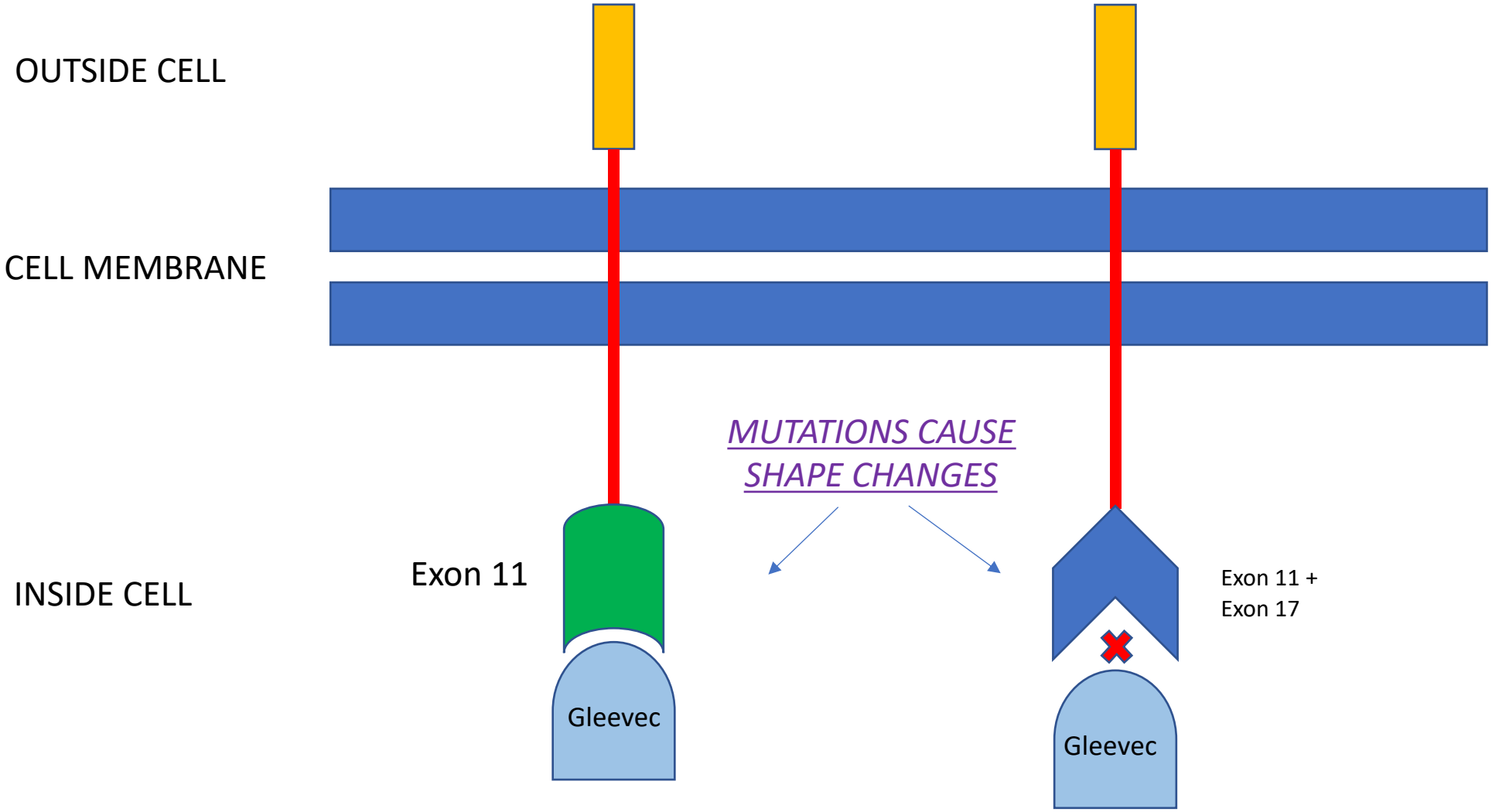
KIT and *PDGFRA* mutations and correlation to protein structure



Pierotti, M. A. *et al.* (2011) Targeted therapy in GIST: *in silico* modeling for prediction of resistance
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2011.3

nature REVIEWS CLINICAL ONCOLOGY

WHY DO MUTATIONS CAUSE RESISTANCE TO DRUGS?



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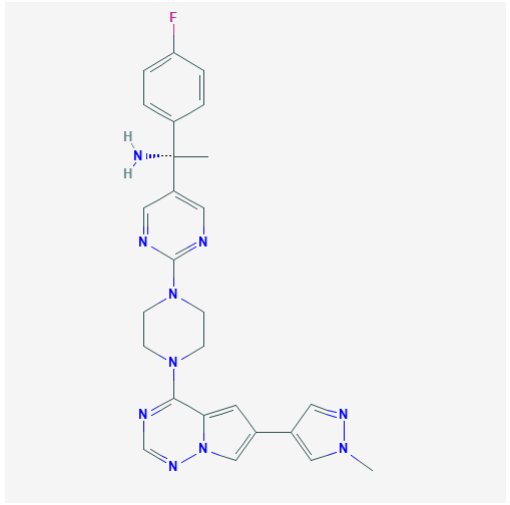
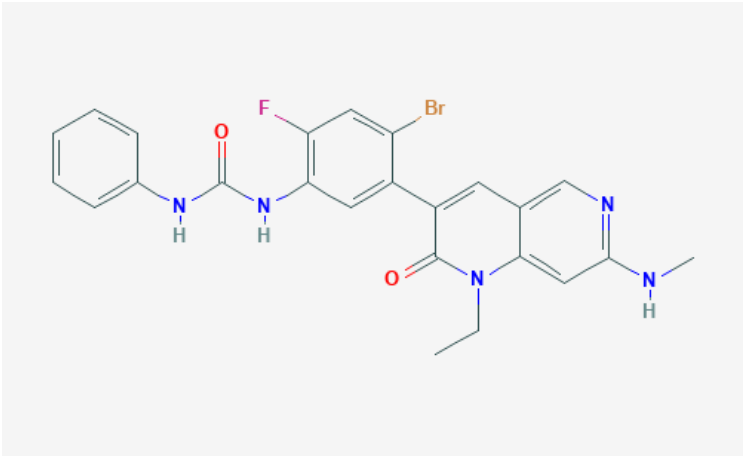
- AVAPRITINIB (AYVAKIT)

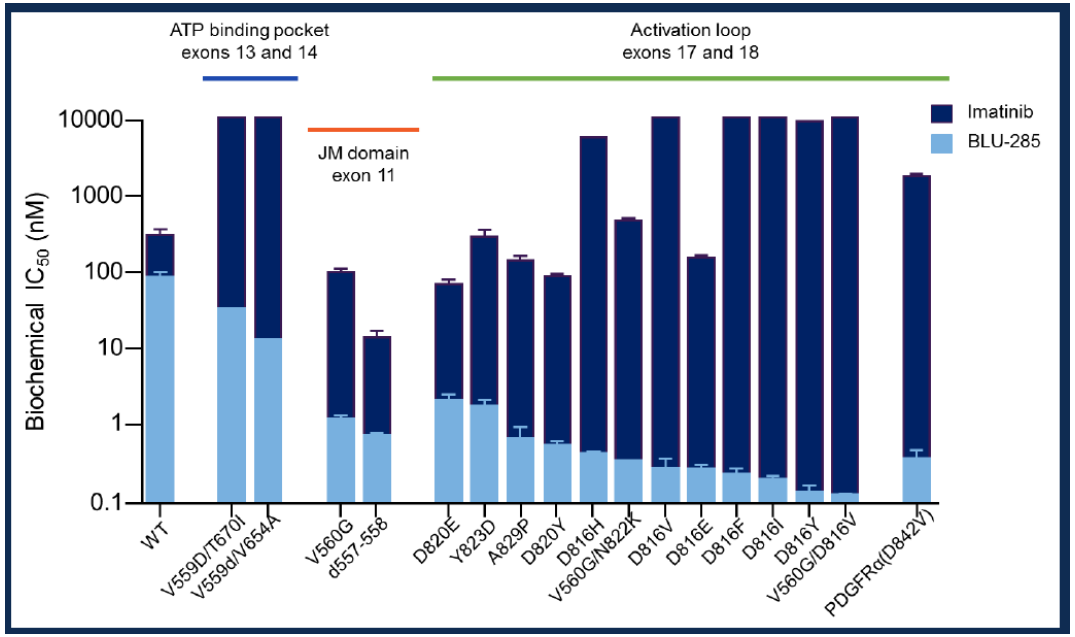


FOCUS ON :

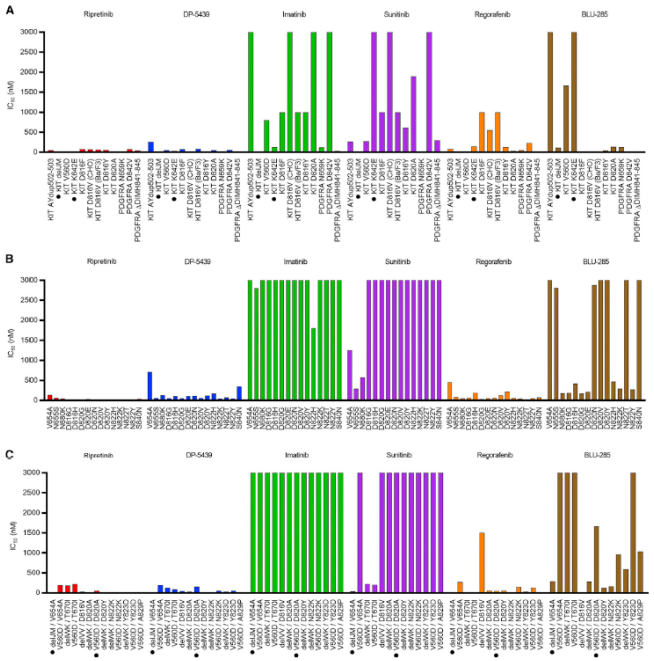
- RIPRETINIB (QINLOCK)
- AVAPRITINIB (AYVAKIT)

- RIPRETINIB (QINLOCK)



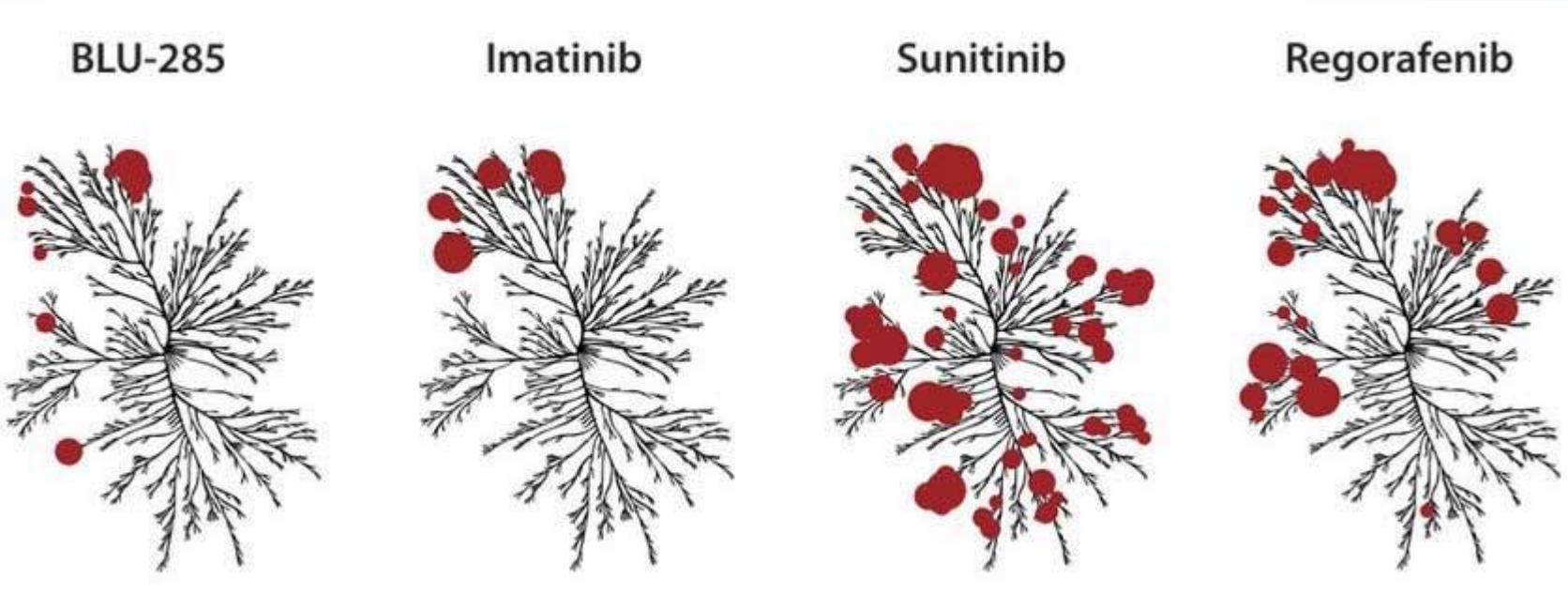


MC Heinrich et. Al.



Cancer Cell *35*, 738–751, May 13, 2019

Avapritinib: Type I kinase receptor inhibitor, inhibits at the activation loop PDGFRa and KIT



Type I kinase receptor inhibitor, inhibits at the activation loop

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Oncology

ARTICLES | VOLUME 21, ISSUE 7, P935-946, JULY 01, 2020

Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial

Michael C Heinrich, MD † • Robin L Jones, MD † • Prof Margaret von Mehren, MD † • Prof Patrick Schöffski, MD • César Serrano, MD • Prof Yoon-Koo Kang, MD • Philippe A Cassier, MD • Olivier Mir, MD • Ferry Eskens, MD • William D Tap, MD • Prof Piotr Rutkowski, MD • Sant P Chawla, MD • Prof Jonathan Trent, MD • Meera Tugnait, PhD • Erica K Evans, PhD • Tamieka Lauz, MS • Teresa Zhou, PhD • Maria Roche, MS • Beni B Wolf, MD • Prof Sebastian Bauer, MD † • Prof Suzanne George, MD † • Show less • Show footnotes

Published: July, 2020 • DOI: https://doi.org/10.1016/S1470-2045(20)30269-2 • Check for updates

Summary

Background

Targeting of KIT and PDGFRA with imatinib revolutionised treatment in gastrointestinal stromal tumour; however, PDGFRA Asp842Val (D842V)-mutated gastrointestinal stromal tumour is highly resistant to tyrosine kinase inhibitors. We aimed to ass safety, tolerability, and antitumour activity of avapritinib, a novel KIT and PDGFRA inhibitor that potently inhibits PDGFRA D

Avapritinib (AYVAKIT)- Data in PDGFRA exon 18 Mutation

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- On January 9, 2020, the FDA approved Avapritinib (AYVAKIT) for adults with unresectable or metastatic GIST harboruing a PDGFRA exon 18 mutation, including D842V mutations
- First therapy approved for GIST patients harboring a PDGFRA exon 18 mutation
- Efficacy was investigated in NAVIGATOR (NCT02508532), a multi-center, single-arm, open-label trial enrolling 43 patients with GIST harboring a PDGFRA exon 18 mutation, including 38 patients with PDGFRA D842V mutations
- For patients harboring a PDGFRA exon 18 mutation, the ORR was 84% (7% complete responses and 77% partial responses). For the subgroup of patients with **PDGFRA D842V** mutations, the **ORR was 89%** (8% complete responses and 82% partial responses)
- 61% of the responding patients with exon 18 mutations had a response lasting 6 months or longer (31% of patients with an ongoing response were followed for less than 6 months).
- The most common adverse reactions (incidence ≥ 20%) edema, nausea, fatigue/asthenia, cognitive impairment, vomiting, decreased appetite, diarrhea, hair color changes, increased lacrimation, abdominal pain, constipation, rash and dizziness
- The recommended avapritinib dose is

300 mg orally once daily on an empty stomach,

at least one hour before and two hours after a meal

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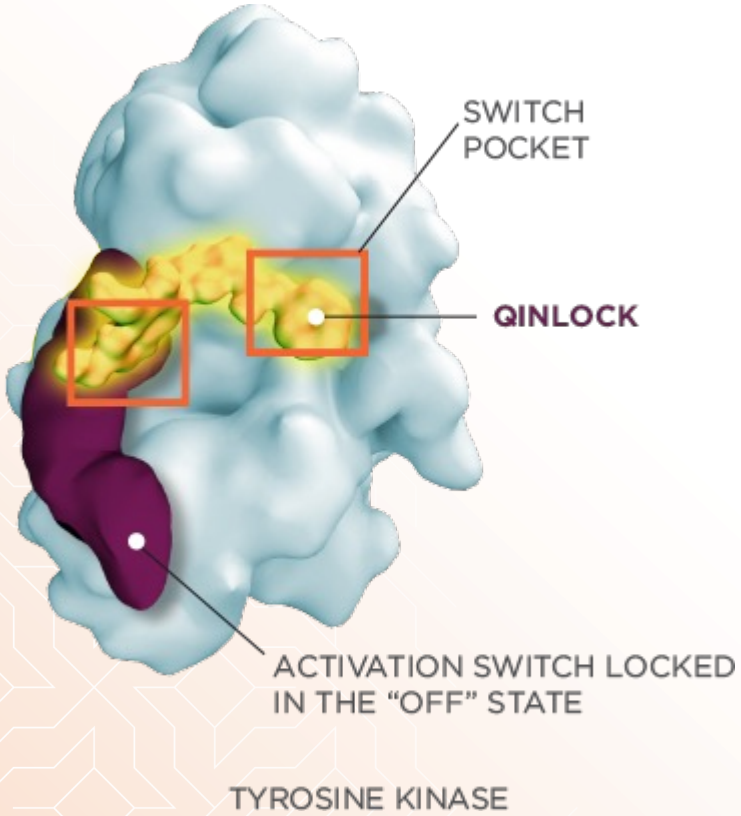
Avapritinib

- VOYAGER Trial: An International, Multicenter, Open-label, Randomized, Phase 3 Study of BLU-285 (Avapritinib) vs Regorafenib in Patients With Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)
- Unfortunately, study did meet it's primary endpoint (improved PFS) which means that it do not work better than Regorafenib
- Need to further explore mutation status as to why
- Regorafenib remains standard 3rd line treatment

Ripretinib: a type 3 kinase inhibitor



Binds to both the activation switch pocket, regardless of where the mutations arise

Locks the kinases in the inactive ("off") state, inhibiting downstream signaling cancer cell proliferation

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Ripretinib: INVICTUS trial Published in *Lancet Oncology* July 2020

Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial

Jean-Yves Blay, César Serrano, Michael C Heinrich, John Zalcberg, Sebastian Bauer, Hans Gelderblom, Patrick Schöffski, Robin L Jones, Steven Attia, Gina D'Amato, Ping Chi, Peter Reichardt, Julie Meade, Kelvin Shi, Rodrigo Ruiz-Soto, Suzanne George, Margaret von Mehren

Patients with advanced (metastatic) GIST who have progressed on Imatinib, Sunitinib and Regorafenib
Could have also had another TKI

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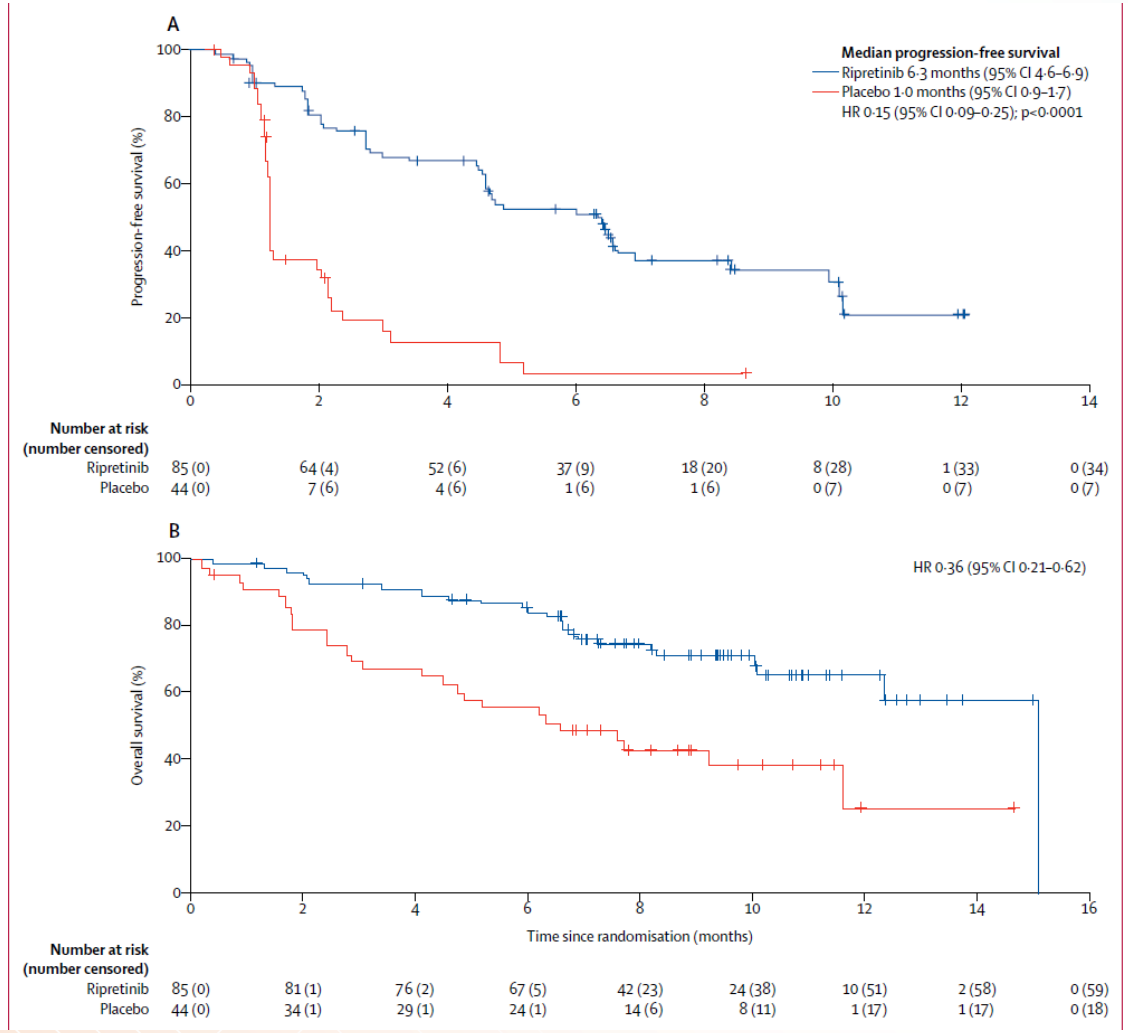

	Ripretinib group (n=85)	Placebo group (n=44)	p value
Confirmed objective response	8 (9%; 4–18)	0 (0%; 0–8)	0·0504
Complete response	0 (0%; 0–4)	0 (0%; 0–8)	..
Partial response	8 (9%; 4–18)	0 (0%; 0–8)	..
Stable disease (6 weeks)	56 (66%; 55–76)	9 (95%; 10–35)	..
Stable disease (12 weeks)	40 (47%; 36–58)	2 (5%; 1–16)	..
Progressive disease	16 (19%; 11–29)	28 (64%; 48–78)	..
Not evaluable	4 (5%)	3 (7%)	..
No response assessment	1 (1%)	4 (9%)	..

Data are n (%; 95% CI) or n (%). *Assessed by blinded independent central review.

Table 2: Objective response rate*

FOR DOCTORS: Improved response, stable disease, progressive free survival and overall all survival, improved QOL, compared to placebo

FOR PATIENTS: IT WORKS GREAT!!!

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Cancer Center
A Cancer Center Designated by the National Cancer Institute

On May 15, 2020 FDA approved ripretinib (Qinlock) for adult patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with 3 or more kinase inhibitors including imatinib

Ripretinib (Qinlock)

- Dose is 150 mg (three 50 mg pills once daily) with or without food
- Common (20%) side effects include:
  - Hair loss
  - Fatigue
  - Nausea/vomiting
  - Abdominal pain
  - Constipation or diarrhea
  - Muscle pain
  - Palmar-plantar erythodysesthsia syndrome

  Uncommon but possible serious:
  - New skin cancers
  - High blood pressure
  - Heart problems (cardiomyopathy)

Summary

- Now 5 FDA treatments approved for GIST patients with a handful others also shown to be effective (Pazopanib (Votrient) , Dasatinib (Sprycel), Nilotinib (Tasigna), Sorafenib (Nexavaar),…
- Avapritinib and Ripretinib were developed specifically for GIST patients
- Use of GIST mutation analysis either from the tumor biopsy or liquid biopsy (ctDNA from the blood plasma) is extremely important to help decide which treatment is best

Ripretinib

INTRIGUE Trial:

A Phase 3, **Int**erventional, **R**andomized, Multicenter, Open-Label Study of DCC-2618 vs Sunitinib in Patients with Advanced **G**astrointestinal Stromal Tumors after Treatment with Imatinib

Metastatic, measurable, progressed or intolerant to Imatinib

117 international locations, enrolling quickly!

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  Uncommon but possible serious:
  - New skin cancers
  - High blood pressure
  - Heart problems (cardiomyopathy)

Ripretinib

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INTRIGUE Trial:
A Phase 3, **Int**erventional, **R**andomized, Multicenter, Open-Label Study of DCC-2618 vs Sunitinib in Patients with Advanced **G**astrointestinal Stromal Tumors after Treatment with Imatinib

Metastatic, measurable, progressed or intolerant to Imatinib

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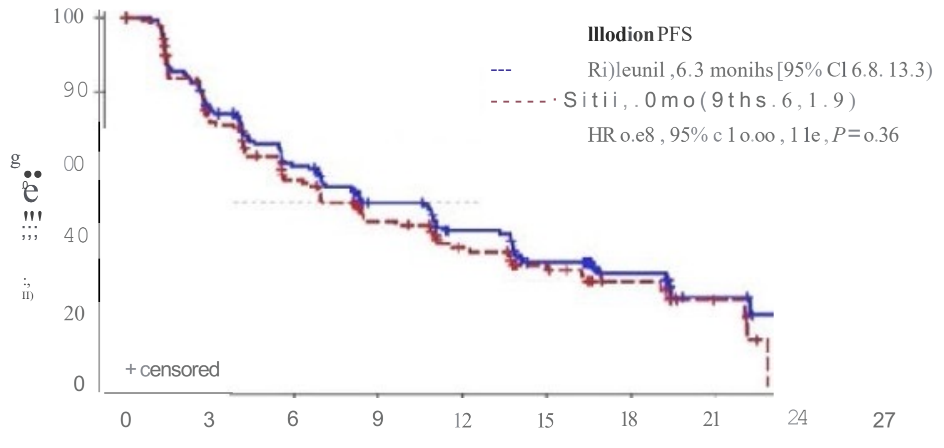
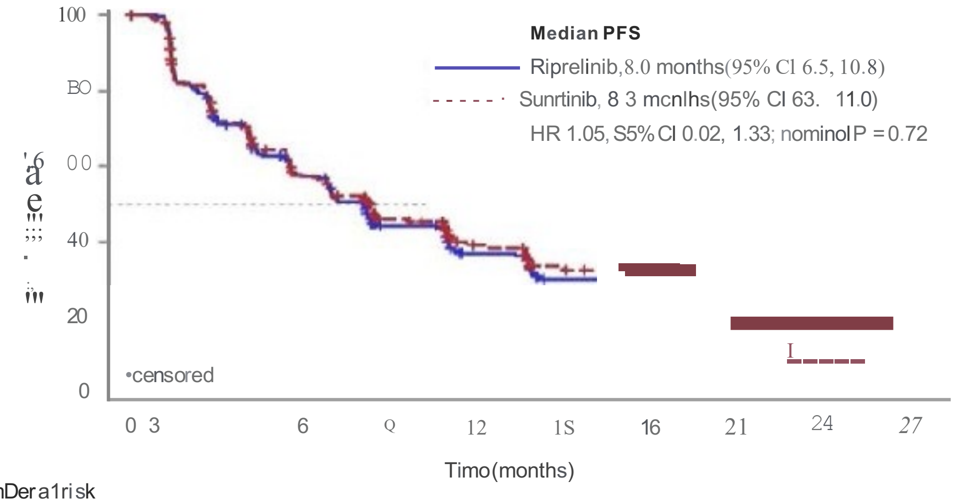
Kaplan-Meier analysis of PFS by IRR

K/T exon 11 ITT



Number at rls										
Ripretinib	163	115	86	61	46	31	18	6	3	0
Sunltinlb	164	104	75	50	33	23	12	S	0	0

AP ITT



NUmDer a1 ri sk										
Rlpretlnlb	226	152	115	75	E6	39	23	10	4	0
Sunltlnlb	227	143	108	88	45	20	16	8		0

- Ripretinib did not meet the primary endpoint of superiority in PFS over sunitinib
- However, the median PFS observed with ripretinib was comparable to the median PFS observed with sunitinib in the exon 11 ITT population (8.3 months vs 7.0 months) and AP ITT population (8.0 months vs 8.3 months)

AP, all patients, C , ,:o ,fidenco in tuv a , H hazarc ra1.10 IRR, 1 1depe,dont radiclogK m111ew ITT mgnt1or: to trga1, PJ="S, progro;s1on suv1val

Heinrich, M.D. Head of tne OHSU Knight Cancer Instituie GIST
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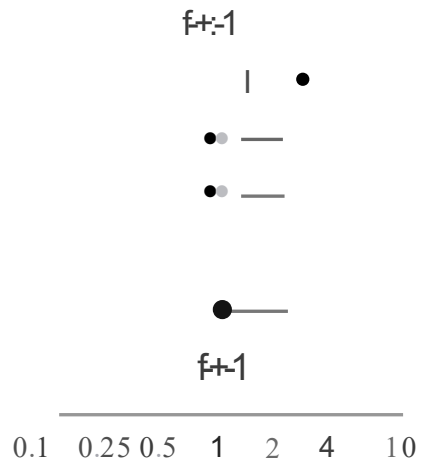
PFS by IRR according to stratification subgroups

	Ripretinib n (events)	Sunitinib n (events)	Median ripretinib (months)	Median sunitinib (months)	Hazard ratio (95% CI)
Overall	226 (146)	227 (130)	8.0	8.3	1.05 (0.82, 1.33)
Mutation type					
KIT exon 11	163 (100)	164 (98)	8.3	7.0	0.88 (0.67, 1.17)
KIT exon 9	31 (27)	29 (14)	5.5	13.8	2.85 (1.48, 5.48)
KIT/PDGFRA WT	15 (9)	18 (10)	7.0	4.1	0.90 (0.36, 2.23)
Other *KIT/PDGFRA*	17 (10)	16 (8)	6.8	8.4	0.90 (0.35, 2.28)
Imatinib intolerance					
Yes	22 (14)	23 (10)	13.7	10.9	1.01 (0.44, 2.33)
No	204 (132)	204 (120)	7.1	8.1	1.02 (0.80, 1.31)



- Subgroup analyses of PFS based on stratification factors (*KIT/PDGFRA* mutation type and imatinib intolerance) revealed that PFS benefit for patients with primary *KIT* exon 9 mutations favored treatment with sunitinib vs ripretinib

CI, confidence interval; IRR, independent radiologic review; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; WT, wild-type.

Michael C. Heinrich, M.D. Head of the OHSU Knight Cancer Institute GIST Translationaland Clinical Research Programs

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IN PURSUIT OF *YOURCURf."*

Conclusions

- Ripretinib did not meet the primary endpoint of superiority in PFS over sunitinib
  - However, the median PFS observed with ripretinib was comparable to the median PFS observed with sunitinib
  - The ORR was higher for patients receiving ripretinib in the *KIT* exon 11 ITT population compared with sunitinib
- Ripretinib had a more favorable safety profile compared with sunitinib
  - Patients receiving ripretinib were less likely to experience Grade 3/4 TEAEs including hypertension, palmar-plantar erythrodysesthesia, diarrhea, and stomatitis compared with patients receiving sunitinib
  - Patients receiving ripretinib were less likely to need dose modification compared with patients receiving sunitinib
  - Patients receiving ripretinib reported better tolerability than patients receiving sunitinib
- Ripretinib may provide meaningful clinical benefit to patients with advanced GIST previously treated with imatinib

GIST, gastrointestinal stromal tumor; ITT, intention-to-treat; ORR, objective response rate; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

PRESENTEDer: Michael C. Heinrich, M.D. Head of the OHSU Knigh: Cancer InstituteGIST Translational and Clinical Research Programs

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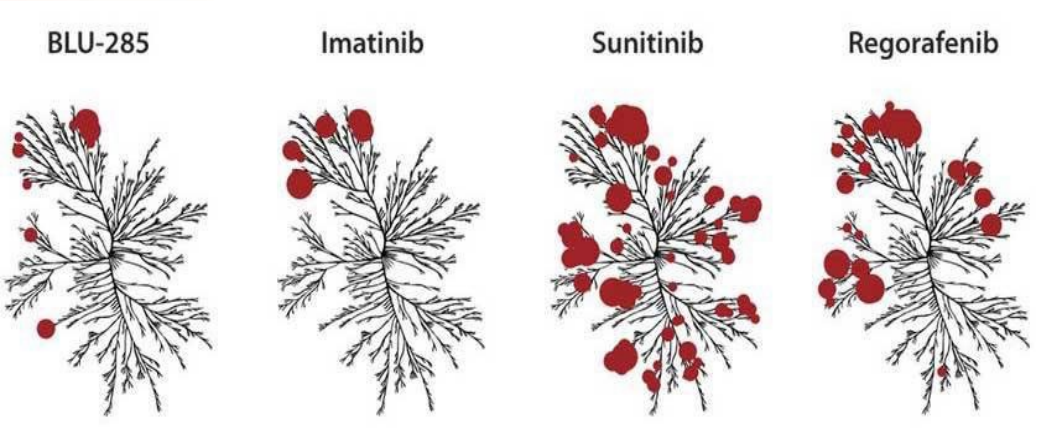
GIST: Avapritinib: Type I kinase receptor inhibitor, inhibits at the activation loop PDGFRa and KIT



Type I kinase receptor inhibitor, inhibits at the activation loop

THE LANCET
Oncology

ARTICLES | VOLUME 21, ISSUE 7, P935-946, JULY 01, 2020

Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial

Michael C Heinrich, MD † • Robin L Jones, MD † • Prof Margaret von Mehren, MD † • Prof Patrick Schöffski, MD • César Serrano, MD • Prof Yoon-Koo Kang, MD • Philippe A Cassier, MD • Olivier Mir, MD • Ferry Eskens, MD • William D Tap, MD • Prof Piotr Rutkowski, MD • Sant P Chawla, MD • Prof Jonathan Trent, MD • Meera Tugnait, PhD • Erica K Evans, PhD • Tamieka Lauz, MS • Teresa Zhou, PhD • Maria Roche, MS • Beni B Wolf, MD • Prof Sebastian Bauer, MD † • Prof Suzanne George, MD † • Show less • Show footnotes

Published: July, 2020 • DOI: https://doi.org/10.1016/S1470-2045(20)30269-2 • Check for updates

Summary

Background

Targeting of KIT and PDGFRA with imatinib revolutionised treatment in gastrointestinal stromal tumour; however, PDGFRA Asp842Val (D842V)-mutated gastrointestinal stromal tumour is highly resistant to tyrosine kinase inhibitors. We aimed to assess the safety, tolerability, and antitumour activity of avapritinib, a novel KIT and PDGFRA inhibitor that potently inhibits PDGFRA D842V, in patients with advanced gastrointestinal stromal tumours, including patients with KIT and PDGFRA D842V-mutant gastrointestinal stromal tumours (NAVIGATOR).

Methods

- Each bar is a patient
- Bars below 0 indicate GIST shrinkage!

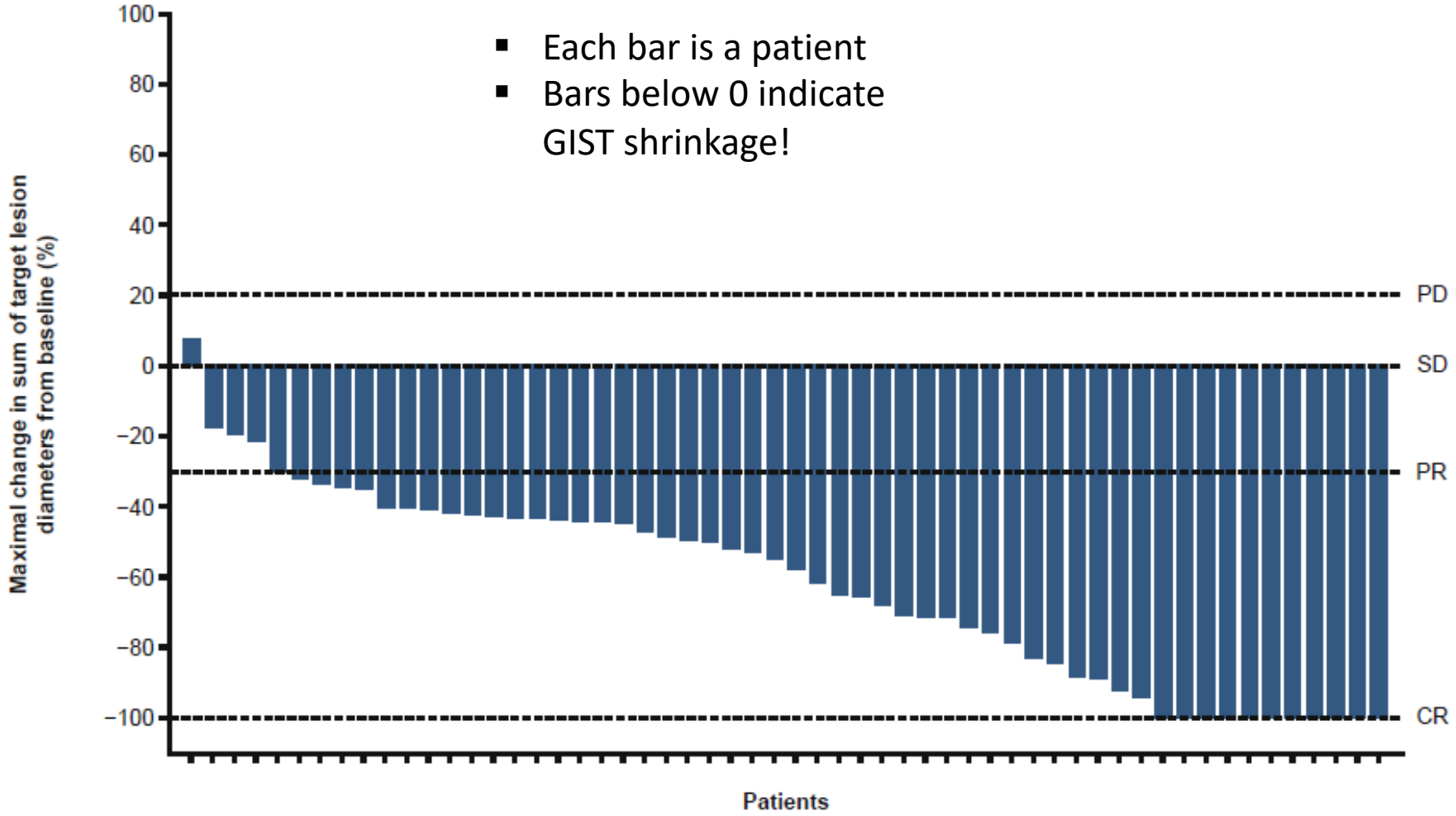


Fig. 3. Maximal percentage change from baseline in sum of target lesion diameters in the *PDGFRA* D842V population. CR, complete response; PD, progressive disease; PDGFRA, platelet-derived growth factor receptor A; PR, partial response; SD, stable disease.

Avapritinib is Very effective for PDGFRA D842V mutated GIST

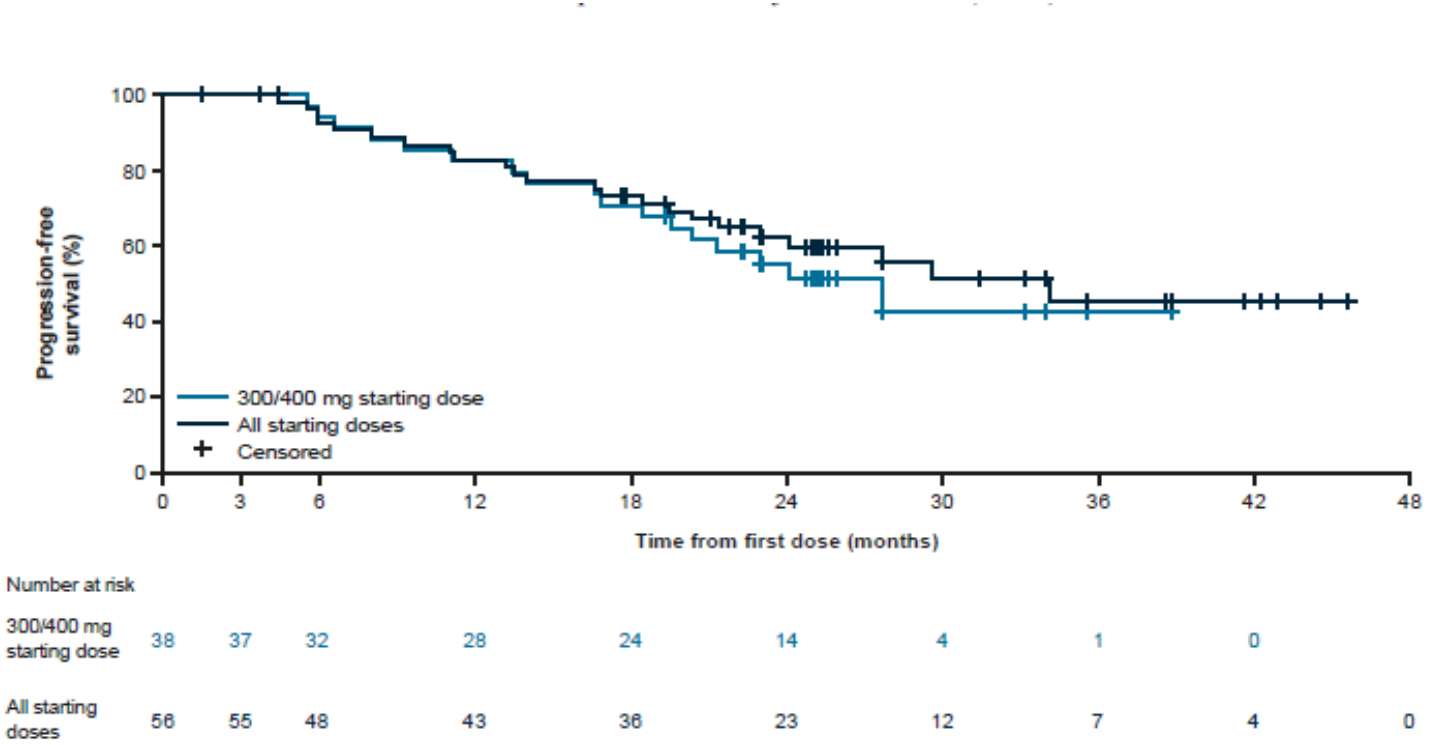


Fig. 5. Progression-free survival in the *PDGFRA* D842V population, PDGFRA, platelet-derived growth factor receptor A.

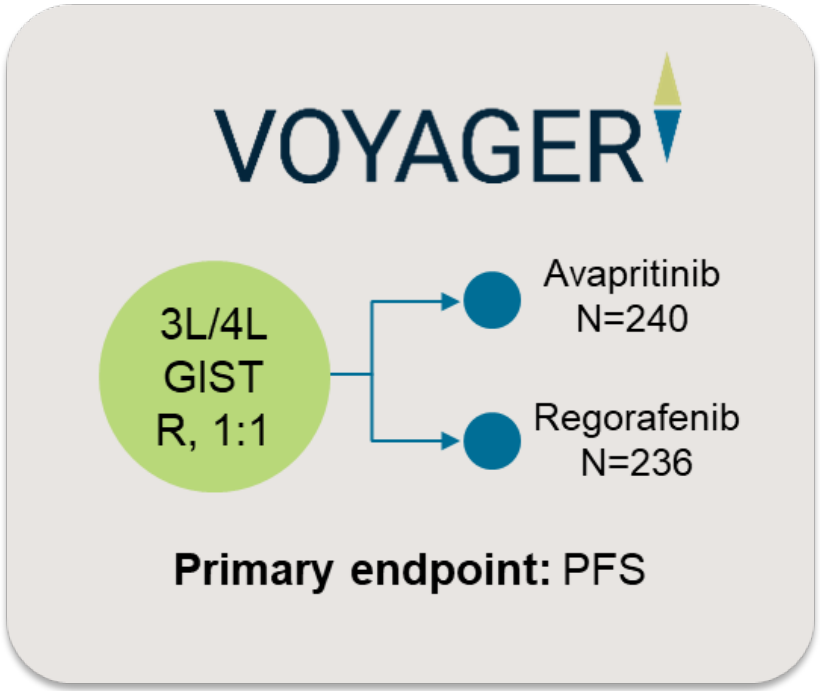
Table 2
Any-cause adverse events occurring in ≥20% of patients in the safety population and the *PDGFRA* D842V population.

Preferred term, n (%)	*PDGFRA* D842V population (n = 56)	Safety population (N = 250)
Nausea	38 (68)	161 (64)
Fatigue	35 (63)	157 (63)
Anaemia	37 (66)	136 (54)
Diarrhoea	37 (66)	112 (45)
Periorbital oedema	27 (48)	110 (44)
Vomiting	21 (38)	106 (42)
Decreased appetite	23 (41)	101 (40)
Increased lacrimation	21 (38)	88 (35)
Memory impairment	23 (41)	81 (32)
Peripheral oedema	21 (38)	80 (32)
Abdominal pain	19 (34)	64 (26)
Constipation	12 (21)	64 (26)
Hair colour changes	16 (29)	62 (25)
Dizziness	16 (29)	59 (24)
Face oedema	13 (23)	57 (23)
Increased blood bilirubin	16 (29)	54 (22)
Hypokalaemia	14 (25)	48 (19)
Headache	13 (23)	48 (19)
Dysgeusia	13 (23)	47 (19)
Decreased weight	15 (27)	46 (18)
Dyspepsia	13 (23)	44 (18)
Cough	15 (27)	39 (16)
Neutropenia	14 (25)	29 (12)
Upper respiratory tract infection	12 (21)	27 (11)

PDGFRA, platelet-derived growth factor receptor A.

Avapritinib Versus Regorafenib in Locally Advanced Unresectable or Metastatic GI Stromal Tumor: A Randomized, Open-Label Phase III Study

Yoon-Koo Kang, MD, PhD[1]; Suzanne George, MD[2]; Robin L. Jones, MD[3]; Piotr Rutkowski, MD, PhD[4]; Lin Shen, MD, PhD[5]; Olivier Mir, MD, PhD, MPH[6]; Shreyaskumar Patel, MD[7]; Yongjian Zhou, MD, PhD[8]; Margaret von Mehren, MD[9]; Peter Hohenberger, MD[10]; Victor Villalobos, MD, PhD[11,12]; Mehdi Brahmi, MD[13]; William D. Tap, MD[14]; Jonathan Trent, MD, PhD[15]; Maria A. Pantaleo, MD, PhD[16]; Patrick Schöffski, MD[17]; Kevin He, PhD[18]; Paggy Hew, MS[18]; Kate Newberry, PhD[18]; Maria Roche, MS[18]; Michael C. Heinrich, MD[19]; and Sebastian Bauer, MD[20]



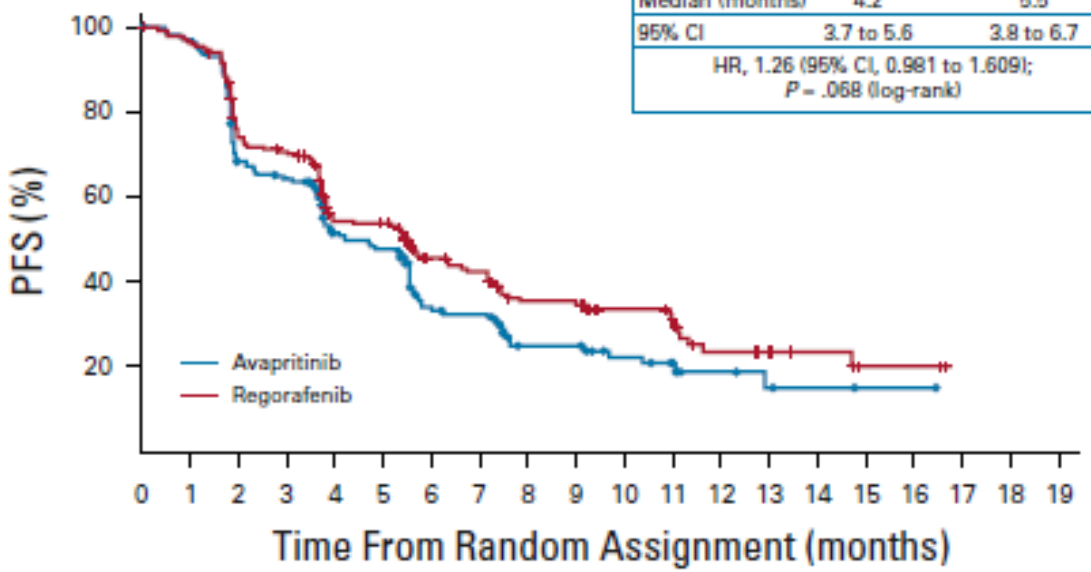
J Clin Oncol 39:3128-3139.

TABLE 1. Demographics and Baseline Characteristics (continued)

Characteristic	Patients		
	Avapritinib (n = 240)	Regorafenib (n = 236)	Total (N = 476)
No. of previous TKIs, No. (%)			
2	207 (86.3)	201 (85.2)	408 (85.7)
3	33 (13.8)	35 (14.8)	68 (14.3)
Previous surgical resection, No. (%)[a]	213 (88.8)	208 (88.1)	421 (88.4)
Total debulking	78 (36.6)	90 (43.3)	168 (39.9)
Partial debulking	116 (54.5)	120 (57.7)	236 (56.1)
Others	75 (35.2)	65 (31.3)	140 (33.3)
Baseline ctDNA, No. (%)[b]			
PDGFRA exon 18	11 (4.6)	7 (3.0)	18 (3.8)
PDGFRA D842V	7 (2.9)	6 (2.5)	13 (2.7)
PDGFRA exon 18 not D842V	4 (1.7)	1 (< 1)	5 (1.1)
KIT V654A/T670I (no *PDGFRA* exon 18 mutation)	33 (13.8)	34 (14.4)	67 (14.1)
KIT exon 17 (no *PDGFRA* exon 18 or *KIT* V654A/T670I mutations)	49 (20.4)	60 (25.4)	109 (22.9)
Others[c]	80 (33.3)	66 (28.0)	146 (30.7)
Unknown	67 (27.9)	69 (29.2)	136 (28.6)

3L Treatment

	Avapritinib (n = 207)	Regorafenib (n = 201)
Events, No.	133	121
Median (months)	4.2	5.5
95% CI	3.7 to 5.6	3.8 to 6.7
HR, 1.26 (95% CI, 0.981 to 1.609); *P* = .068 (log-rank)		



J Clin Oncol 39:3128-3139.

Avapritinib

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VOYAGER Trial: An International, Multicenter, Open-label, Randomized, Phase 3 Study of BLU-285 (Avapritinib) vs Regorafenib in Patients With Locally Advanced Unresectable or Metastatic Gastrointestinal Stromal Tumor (GIST)

Unfortunately, study did meet it's primary endpoint (improved PFS) which means that it do not work better than Regorafenib

Need to further explore mutation status as to why Regorafenib remains standard 3rd line treatment

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THANK YOU!!

Especially to the PATIENTS for being so PATIENT

The Life Raft GROUP

UCLA Jonsson Comprehensive Cancer Center

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EXTRA SLIDES

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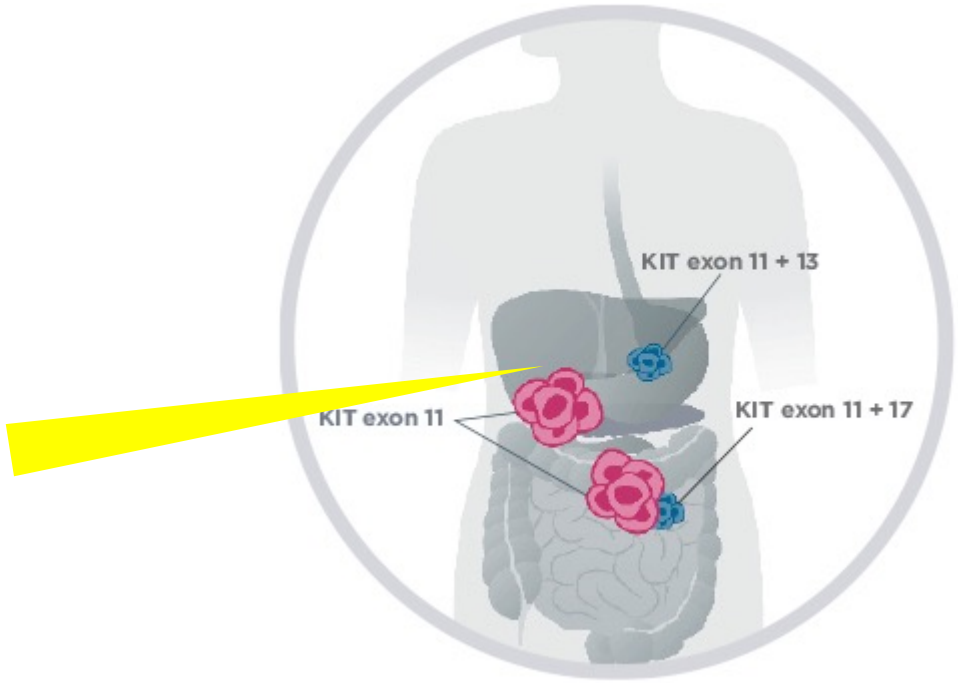
CIRCULATING TUMOR DNA (ctDNA) IN GIST

WHAT INFORMATION DO YOU GET FROM A BIOPSY VERSUS BLOOD?



2022 ASCO® ANNUAL MEETING

Circulating tumor DNA (ctDNA) analyses of the phase III VOYAGER trial: KIT mutational landscape and outcomes in patients with advanced gastrointestinal stromal tumor (GIST)

César Serrano, Sebastian Bauer, David Gómez-Peregrina, Yoon-Koo Kang, Robin L. Jones, Piotr Rutkowski, Olivier Mir, Michael C. Heinrich, William D. Tap, Kate Newberry, Alexandra Grassian, Steve Miller, Hongliang Shi, Patrick Schoffski, Maria Pantaleo, Margaret von Mehren, Jonathan C. Trent, Suzanne George

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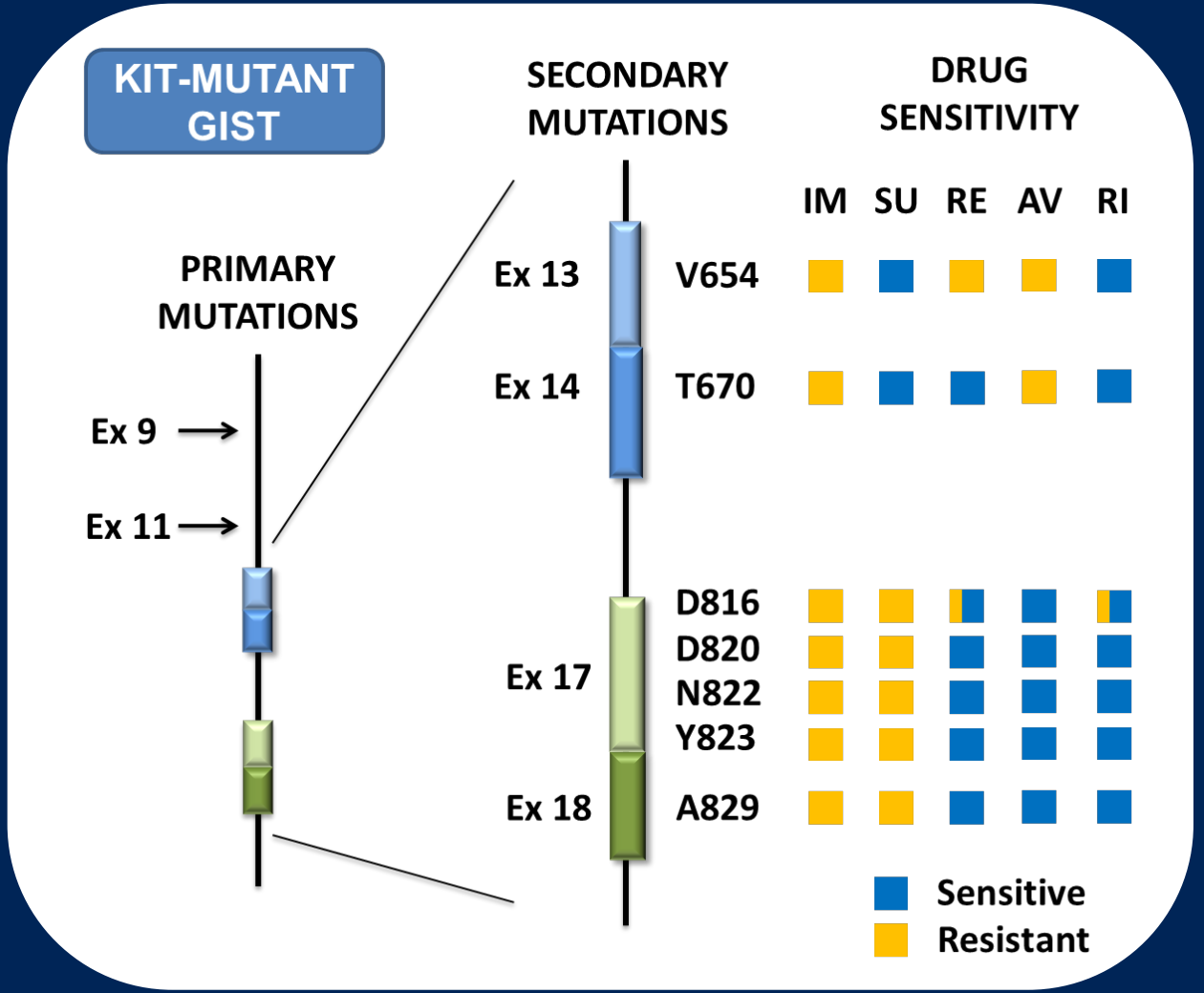
Background TKI-resistance is defined by KIT secondary mutations

- The main mechanism of resistance to imatinib is the emergence of heterogeneous **KIT secondary mutations in ~90% patients**
  - ATP binding pocket (exons 13/14)
  - Activation loop (exons 17/18)
- TKIs after imatinib resistance are effective **only against subsets** of KIT secondary mutations



Modified from Schaefer, DeMatteo & Serrano, *ASCO Ed Book 2022*

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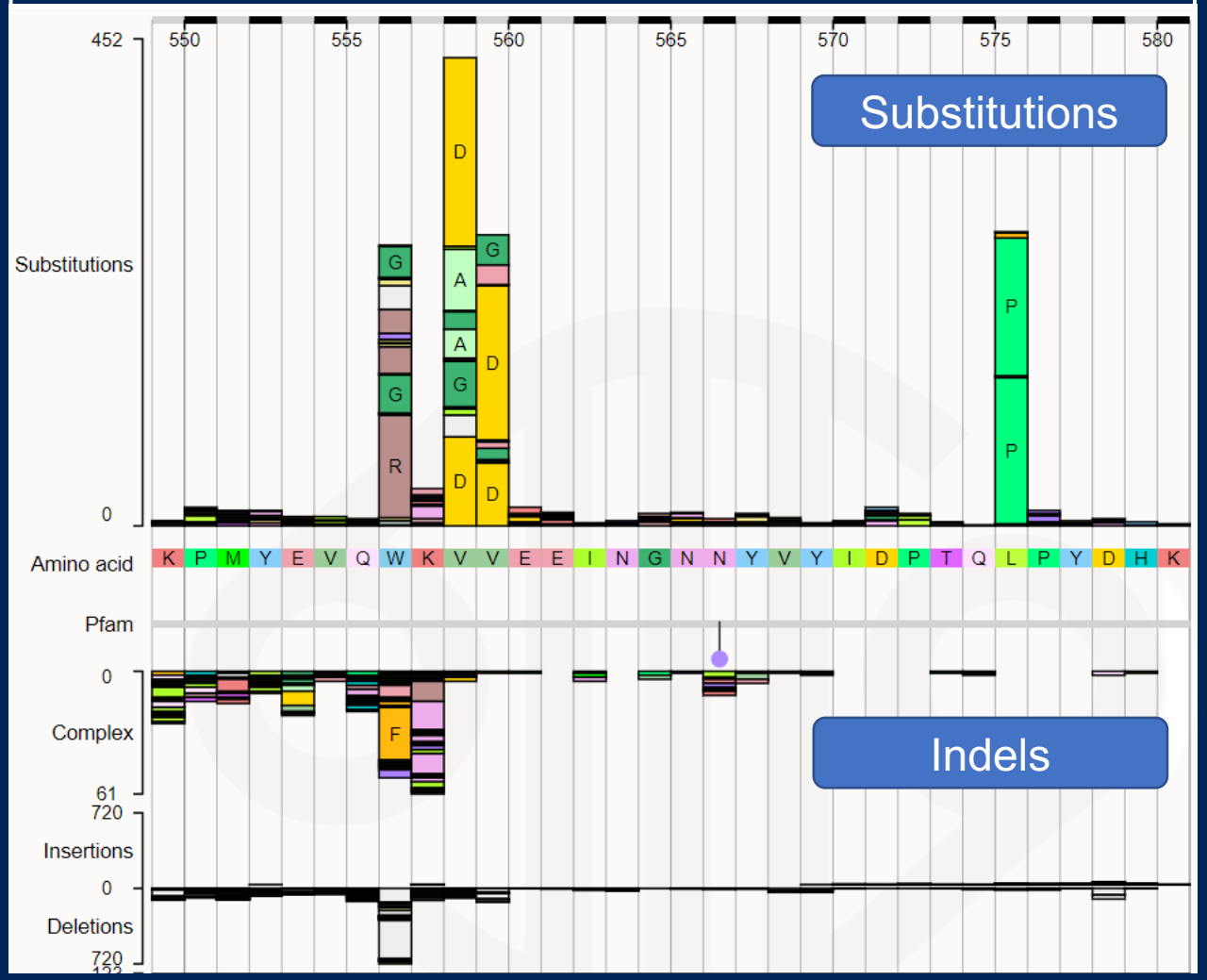
Background ctDNA in GIST

1. **Heterogeneity** in primary and secondary KIT mutations

Genetic alterations affecting *KIT* exon 11



Data obtained from COSMIC

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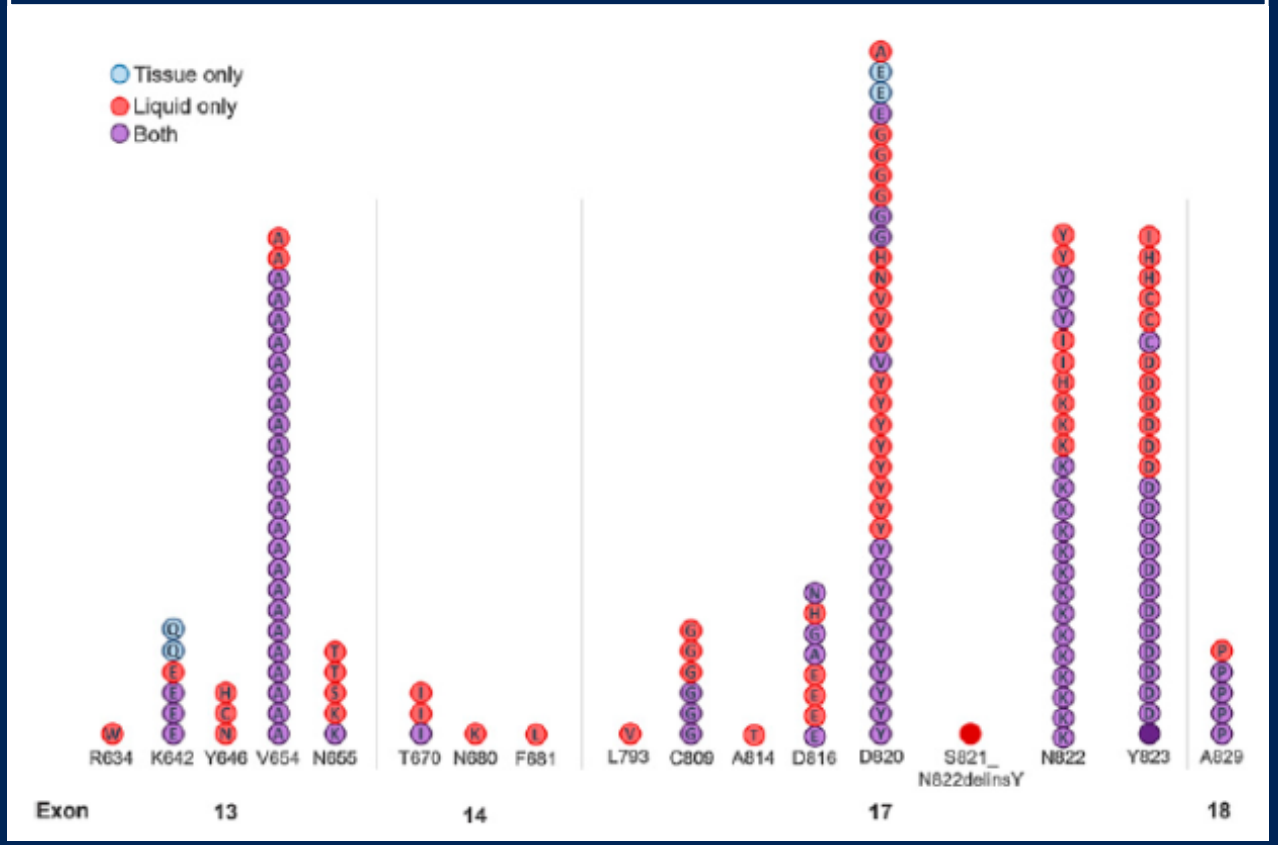
Background ctDNA in GIST

1. **Heterogeneity** in primary and secondary KIT mutations

KIT secondary mutations



Bauer, *Clin Cancer Res* 2021

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Background ctDNA in GIST

1. **Heterogeneity** in primary and secondary KIT mutations

2. ↓ **ctDNA shedding** in GIST

Variable	ctDNA Mutation Positive	Tumor FFPE Mutation Positive	Detection Rate, %
All patients (n = 36)	20	36	56
Primary tumor	0	3	0
Metastatic low burden and responding	0	8	0
Metastatic low burden and progressive	0	5	0
Metastatic high burden and responding	1	1	100
Metastatic high burden and progressive	19	19	100

Arshad, *JCO PO* 2020

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Background ctDNA in GIST

1. **Heterogeneity** in primary and secondary KIT mutations
2. ↓ **ctDNA shedding** in GIST
3. ctDNA has only been explored in **multiple small series,** but with limited data from clinical trials

- **Ph I/II PLX9486 (n=35)**
  » Association with response
- **Ph II Ponatinib (n=45)**
  » Heterogeneity of KIT muts
- **Ph I SuRe (n=14)**
  » Treatment monitoring
- **Various series**
  » Outcomes
  » Treatment guidance

Wagner, *JAMA Oncol* 2021; George, *Clin Can Res* 2022; Serrano, *Clin Can Res* 2019; Namløs, *Mol Can Ther* 2018; Arshad, *JCO PO* 2020; Serrano, *BMC Can* 2020

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Study Design and Methods

- Collection of **plasma samples** from all patients recruited in the VOYAGER phase III clinical trial:
  - Baseline
  - End of Treatment (EoT)

- **ctDNA analysis**: 74-gene panel G360 from Guardant®

> **Landscape of KIT and PDGFRA mutations in advanced GIST**
> **ctDNA & outcomes***

*Cutoff date: March 9, 2020

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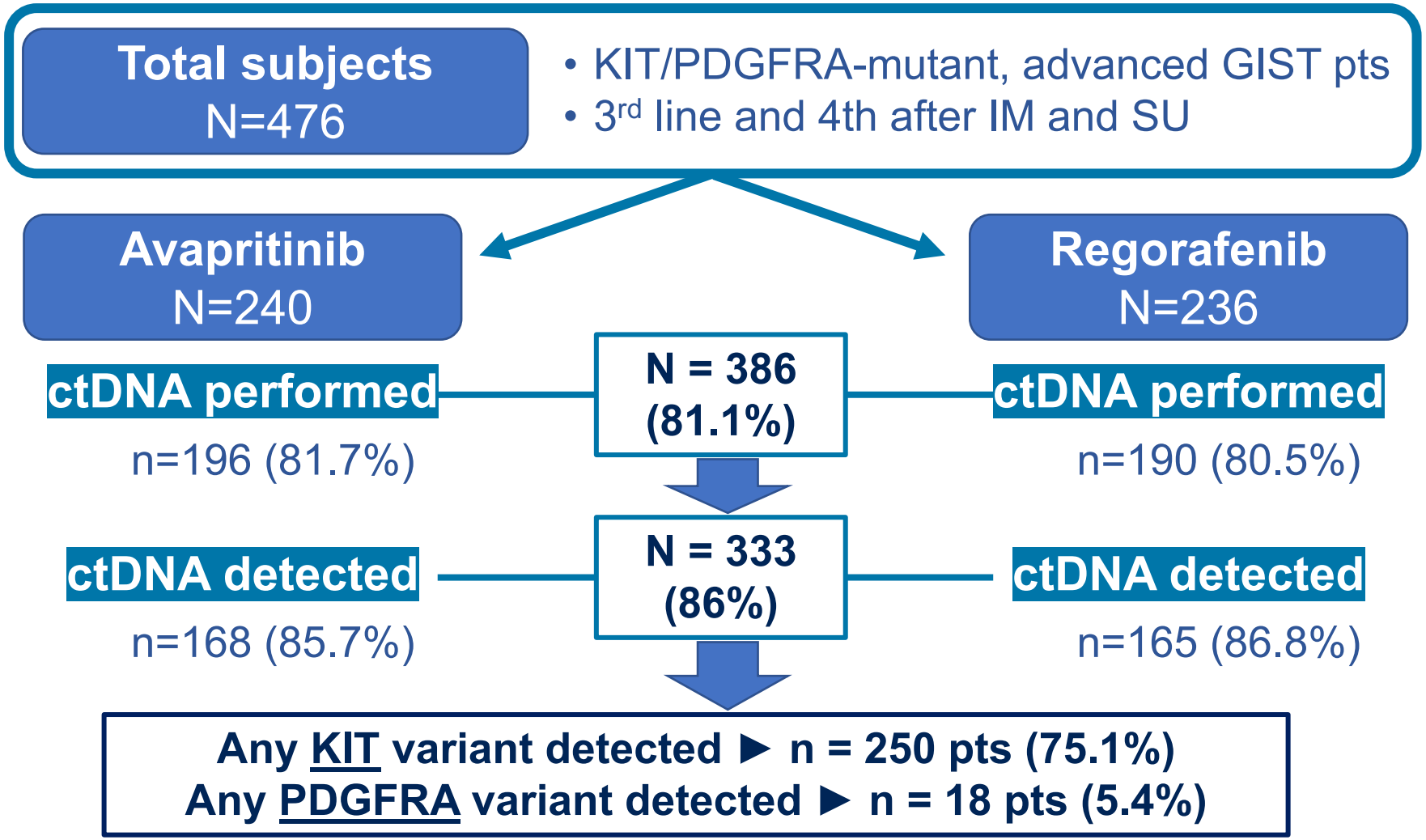
Results: detection of KIT/PDGFRA variants at baseline



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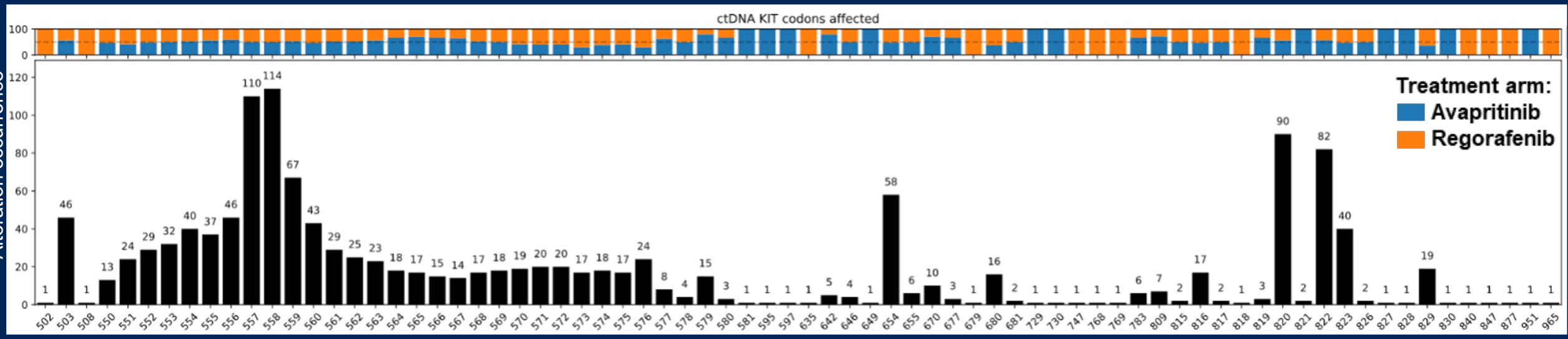
Landscape of KIT mutations: heterogeneity (2)

- **Primary and secondary KIT mutations: codons affected across KIT sequence**



KIT primary mutations | **KIT secondary mutations**

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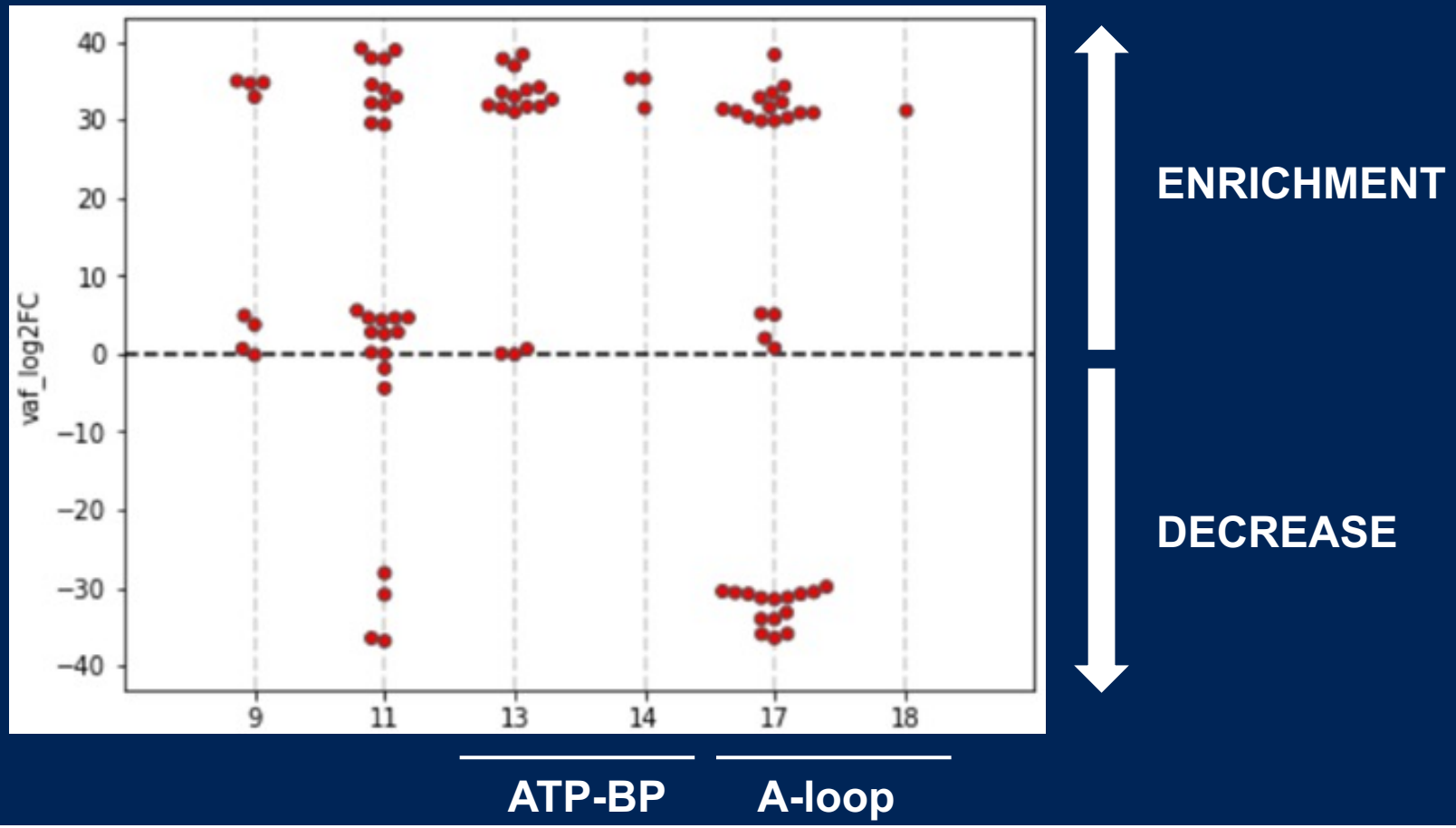
End of Treatment: **Resistance to avapritinib (n=42)**

Enrichment in resistance mutations emerging from the <u>ATP binding pocket (exons 13 and 14)</u> in 42 patients after progression to avapritinib



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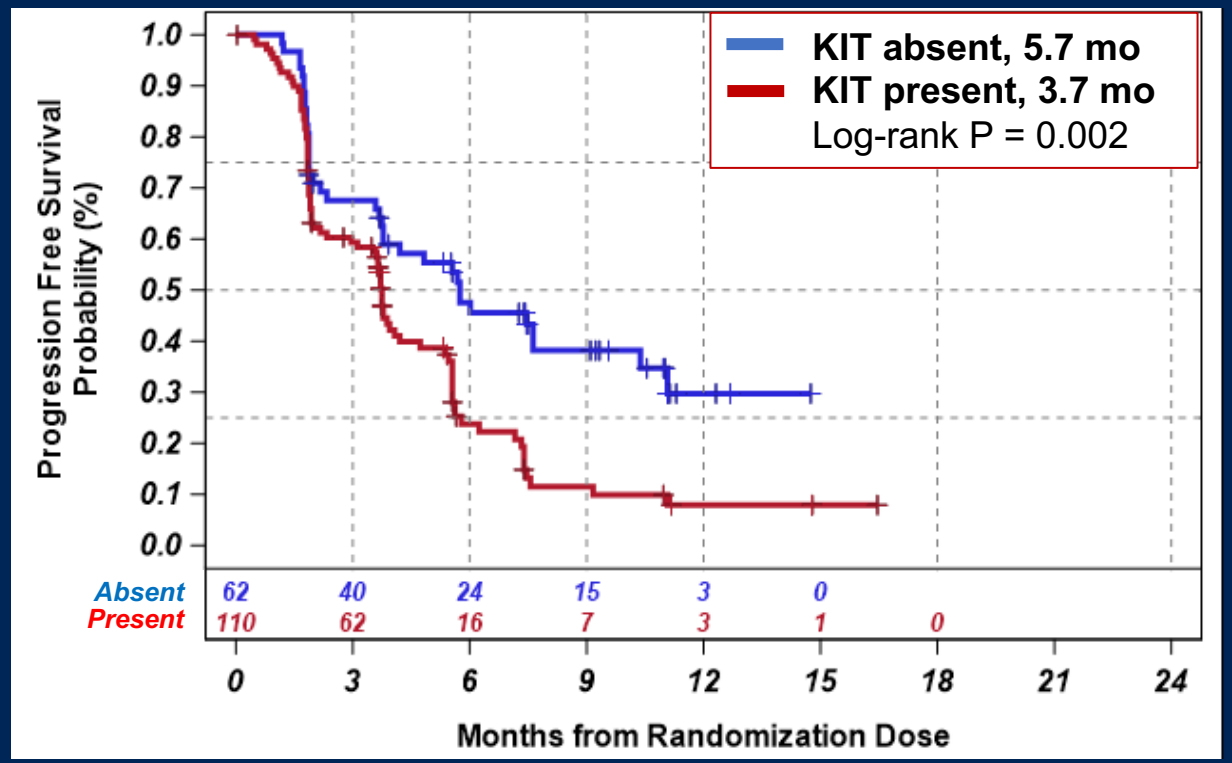
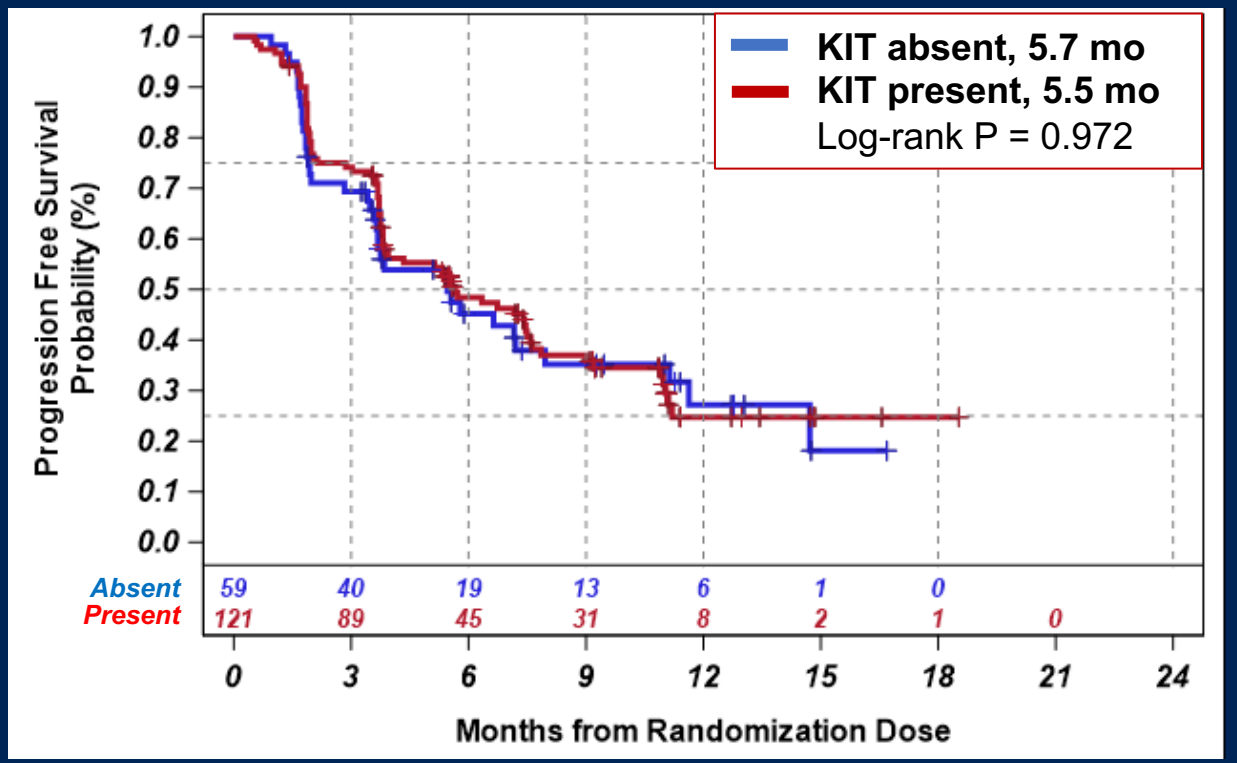
ctDNA mutations & outcomes: **ctDNA negative for KIT mut**

Different PFS behavior among ctDNA KIT negative patients treated with avapritinib (targeted TKI) **v. regorafenib** (multikinase inhibitor)

Median PFS – avapritinib



Median PFS – regorafenib



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