

New Horizons 2020

New Agents for GIST Patients

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GIST Overview

- Most common GI sarcoma
 - 0.2% of all GI tumors, but **80% of GI sarcomas**
- High frequency of **metastatic disease**
- **Gene mutations** drive phenotype and therapy
- Metastatic disease treated with tyrosine kinase inhibitors (**TKIs**)
 - **Imatinib** (PFS = 24 months)
 - **Sunitinib** (PFS = 6 months)
 - **Regorafenib** (PFS = 5 months)



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 - **Avapritinib** (PFS = 3.7 months)



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 - **Avapritinib** (PFS = 3.7 months)
 - **Avapritinib PDGFR** (PFS = NR)



GIST Subtypes

Kit exon 11

Kit exon 9

KIT resistance mutations

Exon 13 (ATP binding site)

Exon 17 (A-loop)

PDGFR D842V

SDH deficiency

Raf V600E

NF-1, Ras

PI3K

IGF-1R expressing

TRK fusion

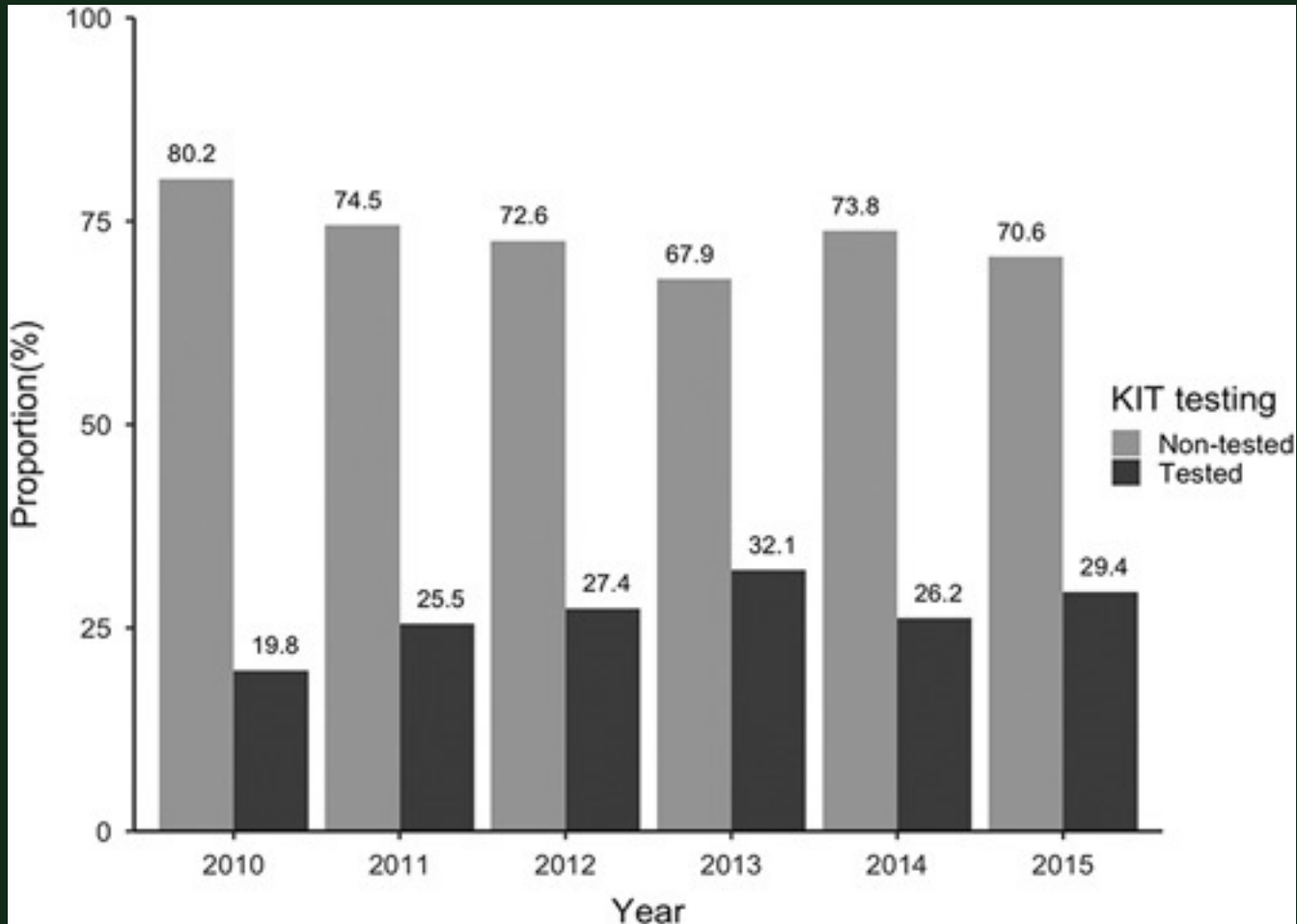


GIST Subtypes and Treatment

- Kit exon 11: Imatinib 400 mg
- Kit exon 9: Imatinib 800mg (or tolerated dose)
- PDGFR D842V: avapritinib
- SDH deficiency: Sunitinib or Regorafenib (TMZ trial)
- Raf V600E: Raf inhibitor
- NF-1, Ras: Raf or Mek inhibitor
- PI3K: mTOR inhibitor
- IGF-1R expressing – IGF-1R inhibitor trial
- TRK fusion – Larotrectenib NTRK inhibitor
- KIT resistance mutations
 - Exon 13 (ATP binding site): Sunitinib 37.5 mg daily
 - Exon 17 (A-loop): Regorafenib or Ripretinib

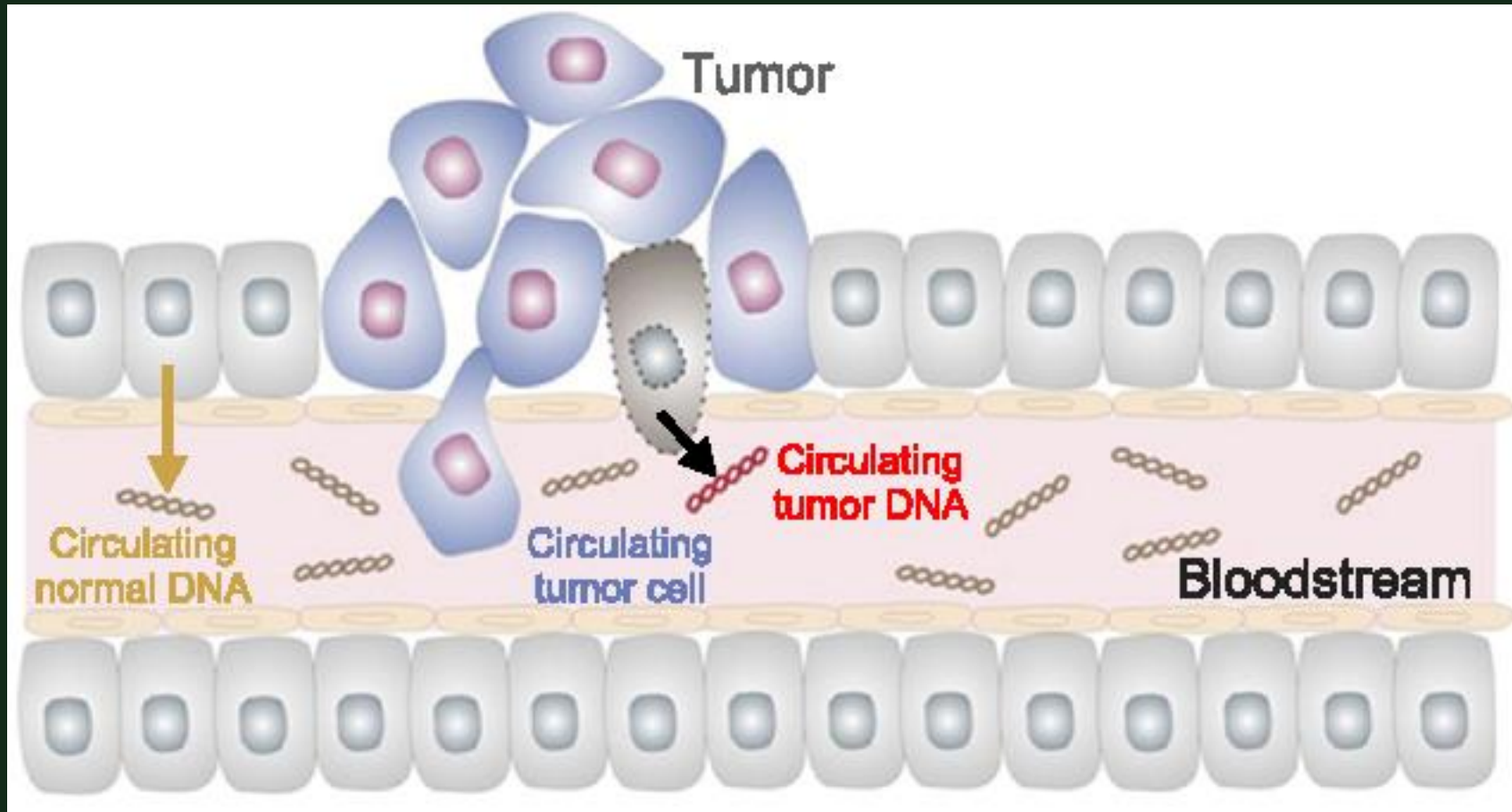


GIST mutation testing in US



Circulating Tumor DNA

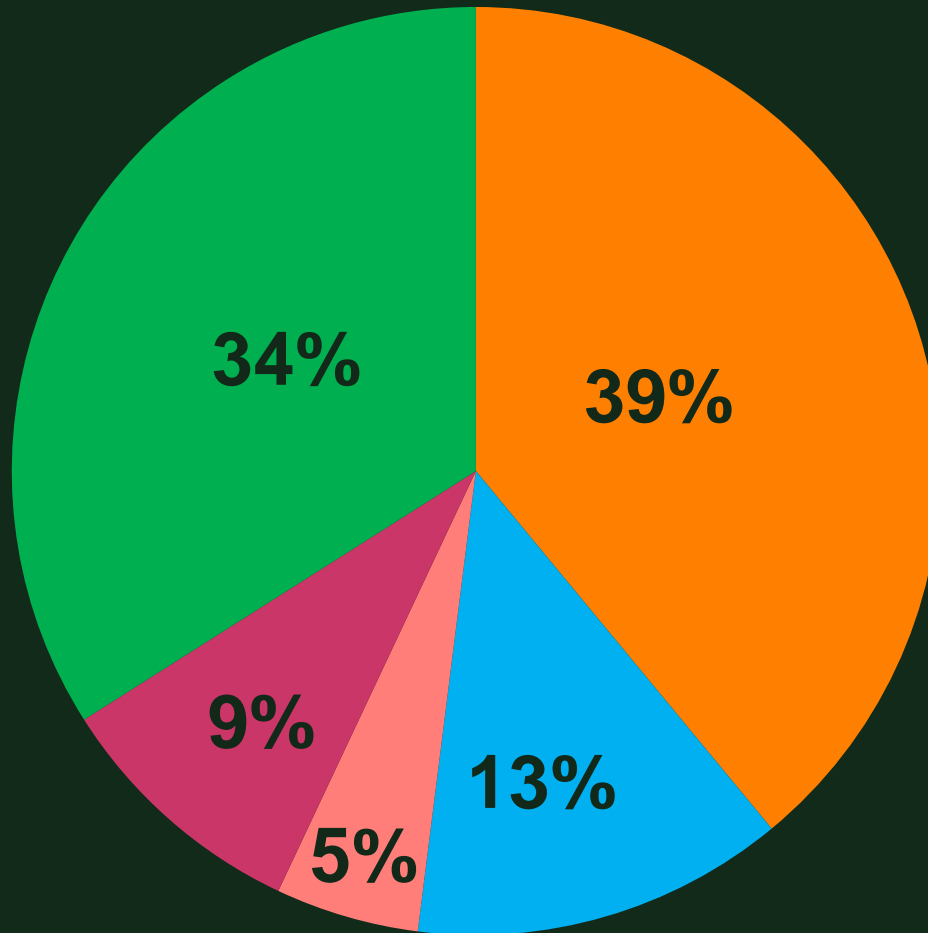
Mutation Testing From Blood (Liquid Biopsy)



Nurwidya et al, 2018
Bauer JCO 2015
Serrano BJC 2018



Distribution of Primary Mutations (%)

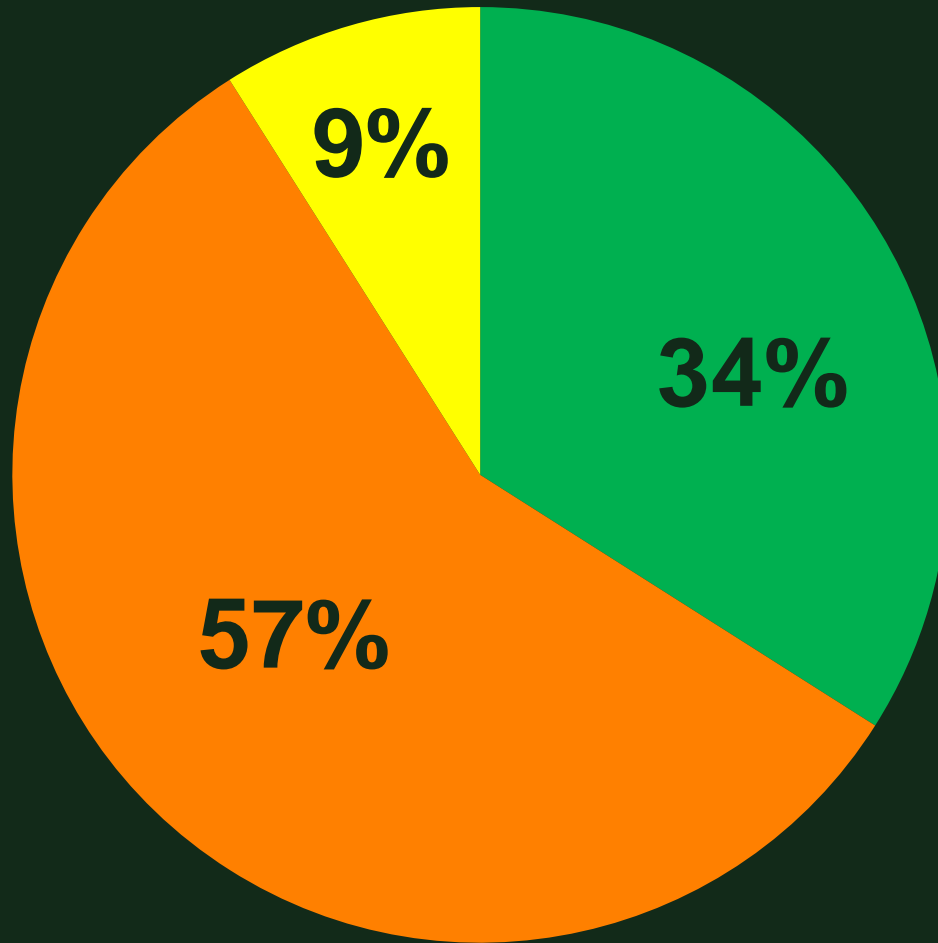


- Patients with mutation (n=162)
- KIT or PDGFR mutations (N=106)
- Not KIT/PDGFR (N=56)

■ Kit exon 11 ■ KIT exon 9 ■ KIT other
■ PDGFR ■ Other



Resistance Mutations (%)



- Patients with KIT or PDGFR mutation (n=106)
- Other: Ras, NF-1, PI3K, TSC

■ KIT Exon 13 ■ KIT Exon 17 ■ Other



Differential Sensitivity to TKI

	Primary Mutations			Resistance Mutations			
	Exon 8	Exon 9	Exon 11	Exon 13	Exon 14	Exon 17	Exon 18
Imatinib	Yellow	Green	Green	Red	Red	Red	Red
Sunitinib	Green	Green	Green	Green	Green	Red	Red
Regorafenib	Yellow	Green	Green	Red	Yellow	Green	Yellow
PLX9486	Green	Green	Green	Yellow	Red	Green	Green
Pexidartinib	Green	Green	Green	Yellow	Green	Yellow	Yellow
Ponatinib	Green	Green	Green	Red	Green	Green	Green
Avapritinib	Green	Green	Green	Red	Yellow	Green	Green
Ripretinib	Green	Green	Green	Yellow	Green	Green	Green

Junaid Arshad, Jonathan C. Trent. JCO Precision Oncology 2020 :4, 66-73

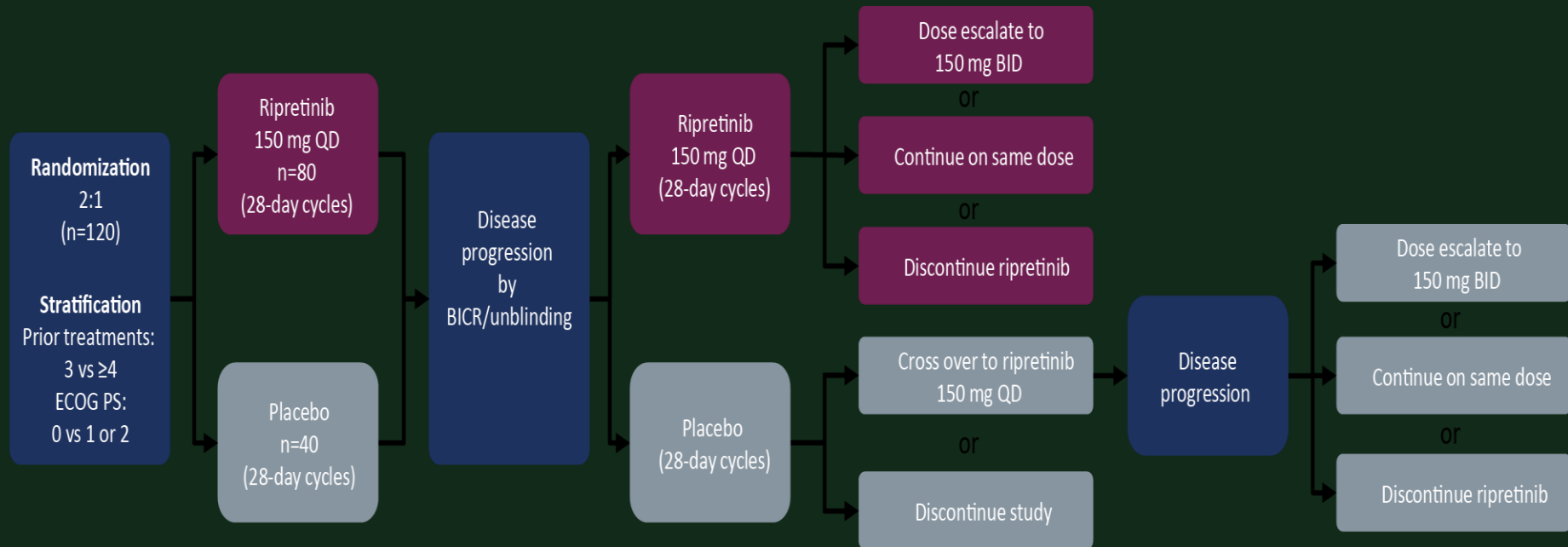
Trent, CTOS 2017; Serrano BJC 2018

Gramza et al, Clinical Cancer Research 15:7510, 2009

Heinrich et al, ASCO 2013 Poster/Abstract 10509



Ripretinib INVICTUS Study Design



Blay JB, et al. *Lancet Oncology*.
Published online June 5, 2020

BICR, blinded independent central review; BID, twice daily; QD once daily.



Data cutoff
May 31, 2019

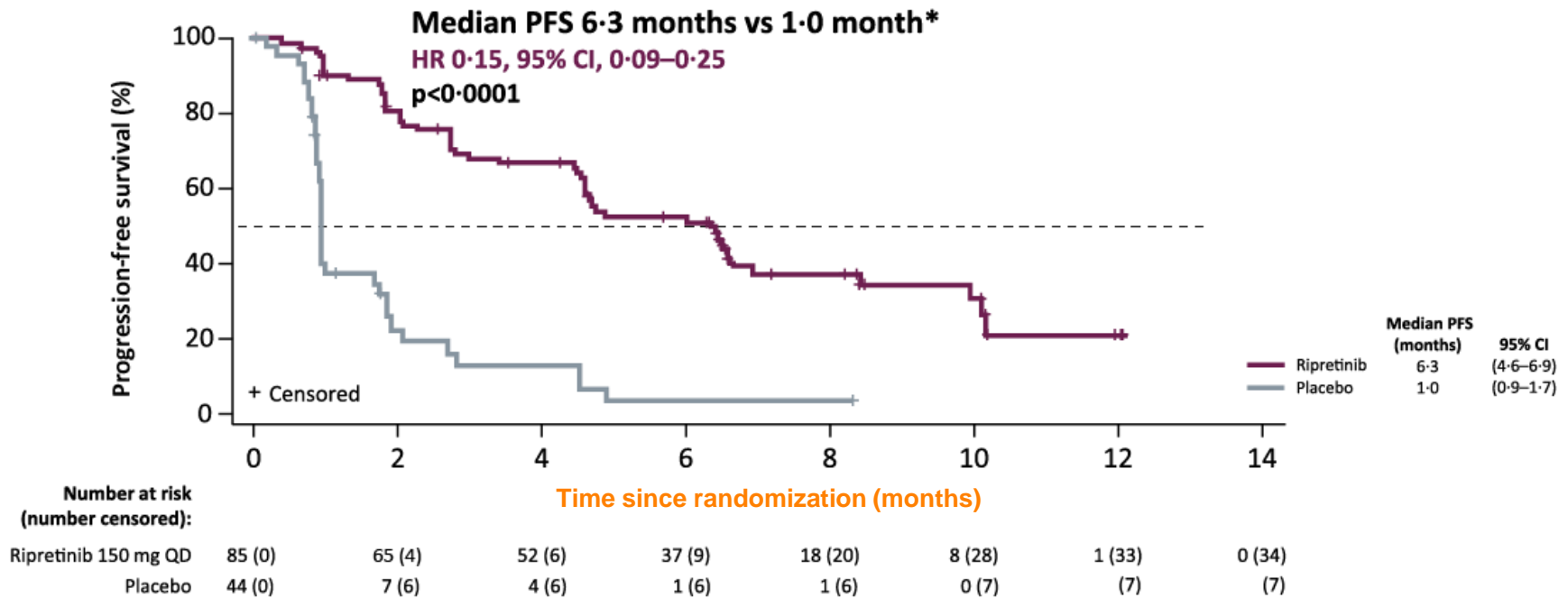


Baseline patient characteristics

Characteristic	Ripretinib (n=85)	Placebo (n=44)
	number of patients (percent)	
Age, median (min, max), y	59 (29, 82)	65 (33, 83)
18–64	57 (67%)	22 (50%)
65–74	20 (24%)	12 (27%)
≥75	8 (9%)	10 (23%)
Sex		
Male	47 (55%)	26 (59%)
Race		
White	64 (75%)	33 (75%)
Region		
United States	40 (47%)	20 (46%)
Number of prior therapies		
3	54 (64%)	27 (61%)
≥4 (range, 4–7)	31 (36%)	17 (39%)
ECOG PS		
0	37 (44%)	17 (39%)
1 or 2	48 (56%)	27 (61%)

Characteristics	Ripretinib (n=85)	Placebo (n=44)
Primary tumor site		
Gastric	40 (47.1%)	18 (40.9%)
Jejunum/ileum	20 (23.5%)	8 (18.2%)
Mesenteric/omental	6 (7.1%)	6 (13.6%)
Other	7 (8.2%)	4 (9.1%)
Duodenum	2 (2.4%)	8 (18.2%)
Colon/rectum	9 (10.6%)	0
Unknown	1 (1.2%)	0
Sum of longest diameters of target lesions (mm), median (range)*	123.1 (28–495)	141.7 (17–412)
Primary mutation (central testing of tumor tissue)		
KIT exon 9	14 (17%)	6 (14%)
KIT exon 11	47 (55%)	28 (64%)
Other KIT	2 (2%)	2 (5%)
PDGFRA	3 (4%)	0
KIT/PDGFRA wild-type	7 (8%)	3 (7%)
Not available/not done†	12 (14%)	5 (11%)

Ripretinib significantly improved mPFS vs. placebo



*Double-blind period.

mPFS of 6.3 months vs 1.0 month
 (HR 0.15, 95% CI 0.09–0.25; p<0.0001)



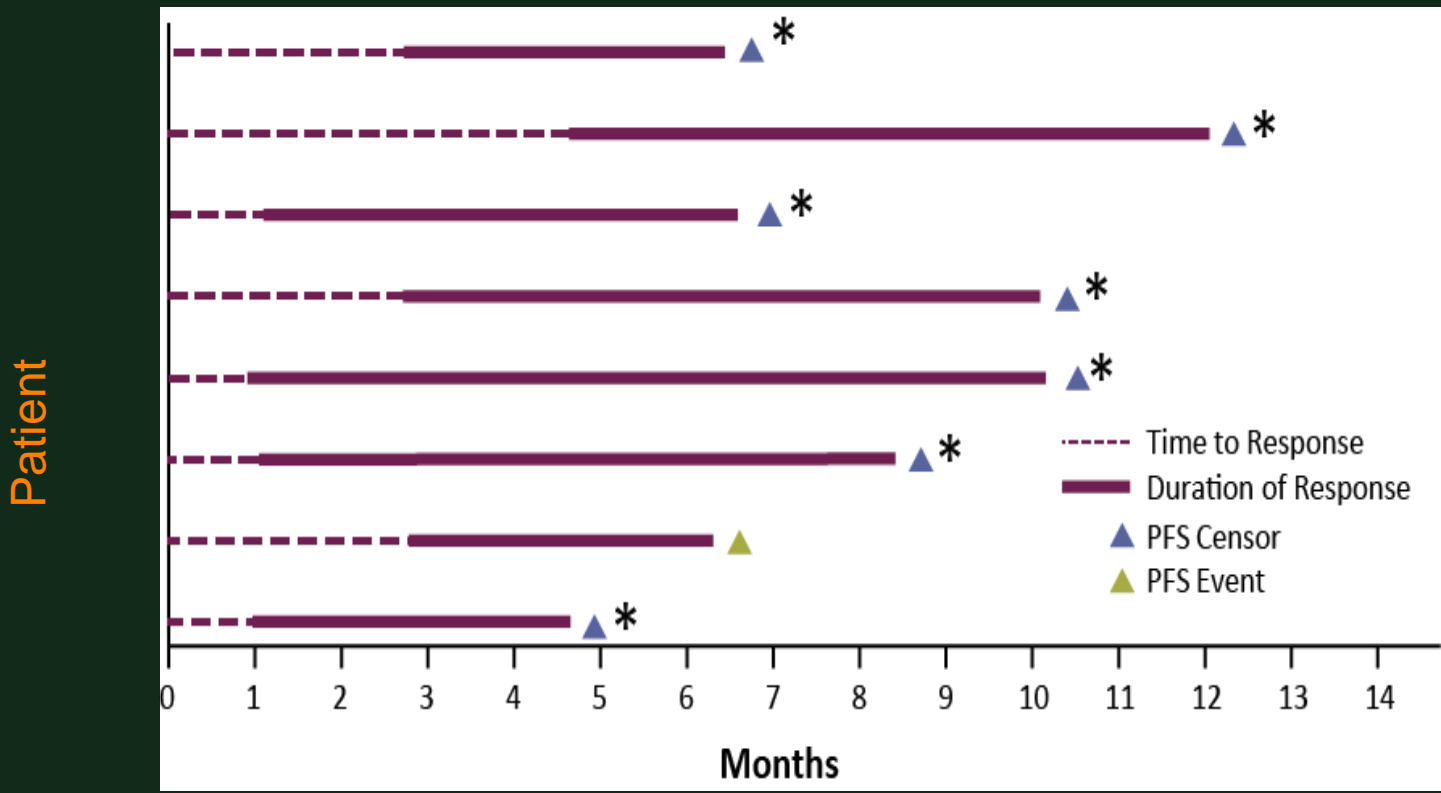
Objective Response Rate

	Ripretinib (n=85) n (%; 95% CI)	Placebo (n=44) n (%; 95% CI)	p value
Confirmed objective response	8 (9%; 4–18)	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 wk	56 (66%; 55–76)	9 (20%; 10–35)	
Stable disease 12 wk	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%)	

- Median time to best response 1.9 months (IQR, 1.0–2.7)
- Median time to progression
 - Ripretinib 6.4 months (95% CI, 4.6–8.4)
 - Placebo 1.0 months (95% CI, 0.9–1.7)



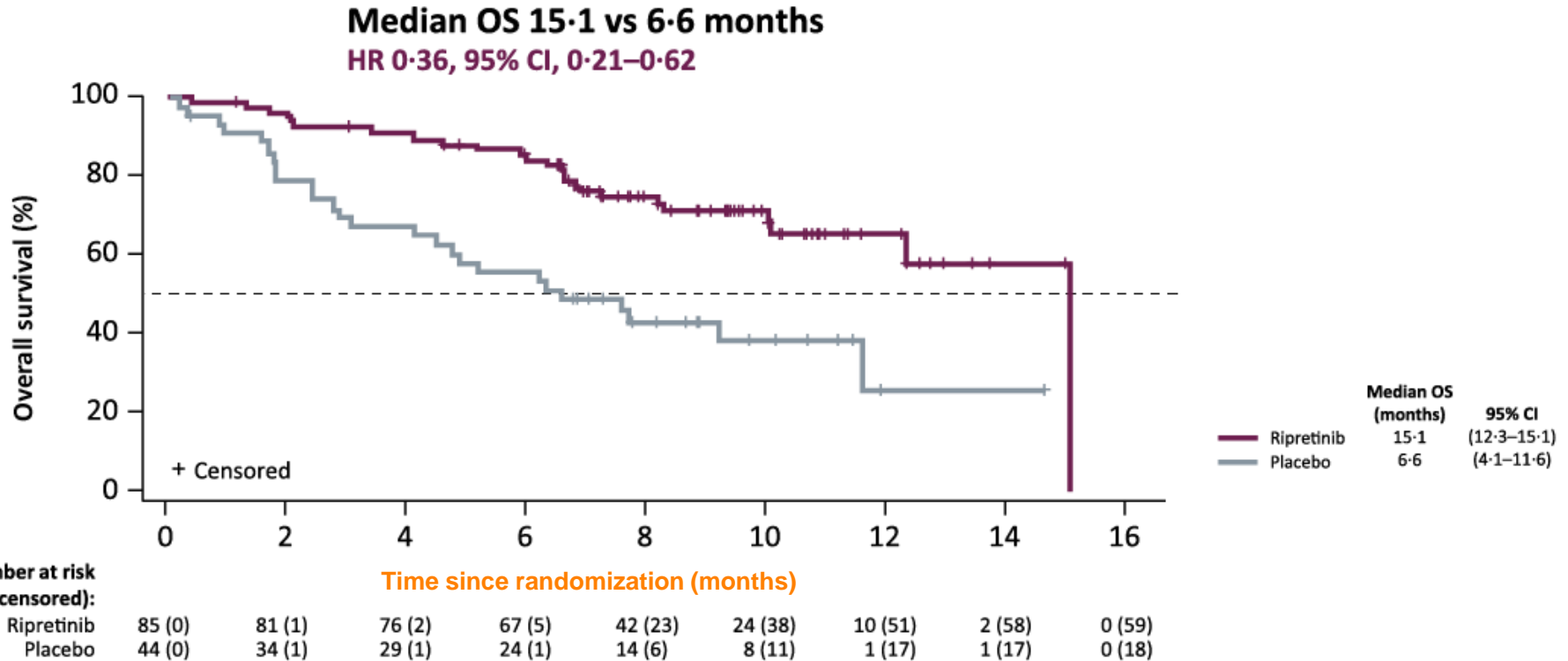
Time to Response and Duration of Response



- Median duration of response not yet reached as of data cutoff
- 1 of the 8 responding patients had disease progression as of data cutoff



Overall Survival*



Events were reported in 26 (30.6%) of 85 patients receiving ripretinib and 26 (59.1%) of 44 patients receiving placebo.

Includes double-blind and open-label periods.

*Owing to hierarchal testing procedures of the endpoints, overall survival could not be formally tested for statistical significance because the objective response was not significant (ORR for ripretinib did not meet our predefined assumption of 22%)



Treatment-Related TEAEs

Preferred Term	Ripretinib (n=85)				Placebo (n=44)*			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Alopecia	42 (49%) [†]	1 (2%)
Myalgia	23 (27%)	1 (1%)	4 (9%)	0
Nausea	21 (25%)	1 (1%)	1 (2%)	0
Fatigue	20 (24%)	2 (2%)	6 (14%)	1 (2%)
PPES	18 (21%) [‡]	0	0	0
Diarrhea	17 (20%)	1 (1%)	0	0	2 (5%)	1 (2%)	0	0
Constipation	13 (15%)	0	0	0	3 (7%)	0	0	0
Decreased appetite	12 (14%)	1 (1%)	0	0	2 (5%)	1 (2%)	0	0
Weight decreased	13 (15%)	0	3 (7%)	0
Blood bilirubin increased	12 (14%)	0	0	..	0	0	0	..
Arthralgia	10 (12%)	0	0	0
Muscle spasms	10 (12%)	0	2 (5%)	0
Hypertension	4 (5%)	3 (4%)	0	0	1 (2%)	0	0	0
Lipase increased	4 (5%)	4 (5%)	0	..	0	0	0	..
Pain in extremity	5 (6%)	1 (1%)	1 (2%)	0
Hypophosphatemia	3 (4%)	2 (2%)	0	0	0	0	0	0
Anemia	2 (2%)	0	0	1 (1%)	0	1 (2%)	2 (5%)	1 (2%)

(Data not shown). Treatment-related TEAEs are listed that occurred in ≥10% of patients in either treatment group or were reported as grade 3, 4, or 5 in either treatment group. *44 patients were randomly assigned to receive placebo, but one patient did not receive treatment.

[†]24 (63%) of 38 women who were given ripretinib had alopecia.

[‡]All PPES events were grade 1 (11 [13%]) or grade 2 (7 [8%]).

GERD, gastroesophageal reflux disease; GI, gastrointestinal; PPES, palmar plantar erythrodysesthesia syndrome.



Treatment-Related TEAEs

Preferred Term	Ripretinib (n=85)				Placebo (n=44)*			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood triglycerides increased	1 (1%)	1 (1%)	0	0	0	0	0	0
Dermatosis	1 (1%)	1 (1%)	0	0	0	0	0	0
Dehydration	1 (1%)	0	0	0	0	1 (2%)	0	0
GERD	1 (1%)	1 (1%)	0	0
Hyperkalemia	0	1 (1%)	0	0	0	1 (2%)	0	0
Hypokalemia	0	1 (1%)	0	0	0	0	0	0
Anal abscess	0	1 (1%)	0	0	0	0	0	0
Ascites	0	1 (1%)	0	0	0	0	0	0
Cardiac failure	0	1 (1%)	0	0	0	0	0	0
Death, reason unknown	1 (1%)	0
Fecaloma	0	1 (1%)	0	0	0	0	0	0
Skin infection	0	1 (1%)	0	0	0	0	0	0
Syncope	..	1 (1%)	0
Upper GI hemorrhage	0	1 (1%)	0	0	0	0	0	0
Acute kidney injury	0	0	0	0	0	1 (2%)	0	0
Pulmonary edema	0	0	0	0	0	0	1 (2%)	0
Septic shock	0	0	..	0	0	1 (2%)

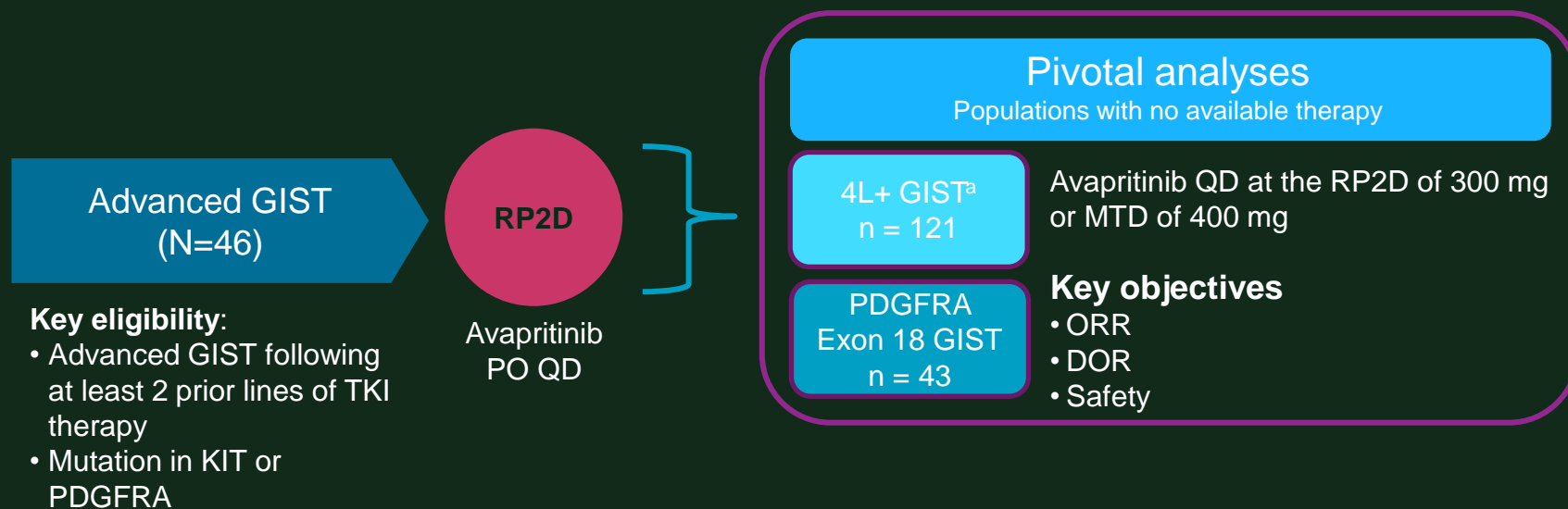
Authors' Discussion: Conclusions

- Results of the **INVICTUS** study showed that ripretinib as fourth-line (or greater than fourth-line) therapy for patients with advance GIST significantly improved median PFS compared with placebo
 - Median PFS with ripretinib was 6.3 months vs 1.0 months with placebo (HR 0.15, 95% CI, 0.09–0.25)
 - The ORR was 9% with ripretinib vs 0% with placebo; however, this result was not significant ($P=0.0504$)
- Ripretinib increased the median overall survival over placebo in both the double-blind and open-label periods. Notably, 29 (66%) of 44 patients in the placebo group crossed over to ripretinib at time of progression, and thus the improvement in overall survival could potentially be underestimated.
- Responses in patients treated with ripretinib were durable, with the median duration of response not yet reached



STUDY DESIGN AND OBJECTIVES

NAVIGATOR is an open-label, dose escalation/dose expansion phase 1 study of avapritinib



Data are based on a data cut-off date of November 16, 2018.

Avapritinib is an investigational agent discovered and currently in development by Blueprint Medicines Corporation



RESULTS

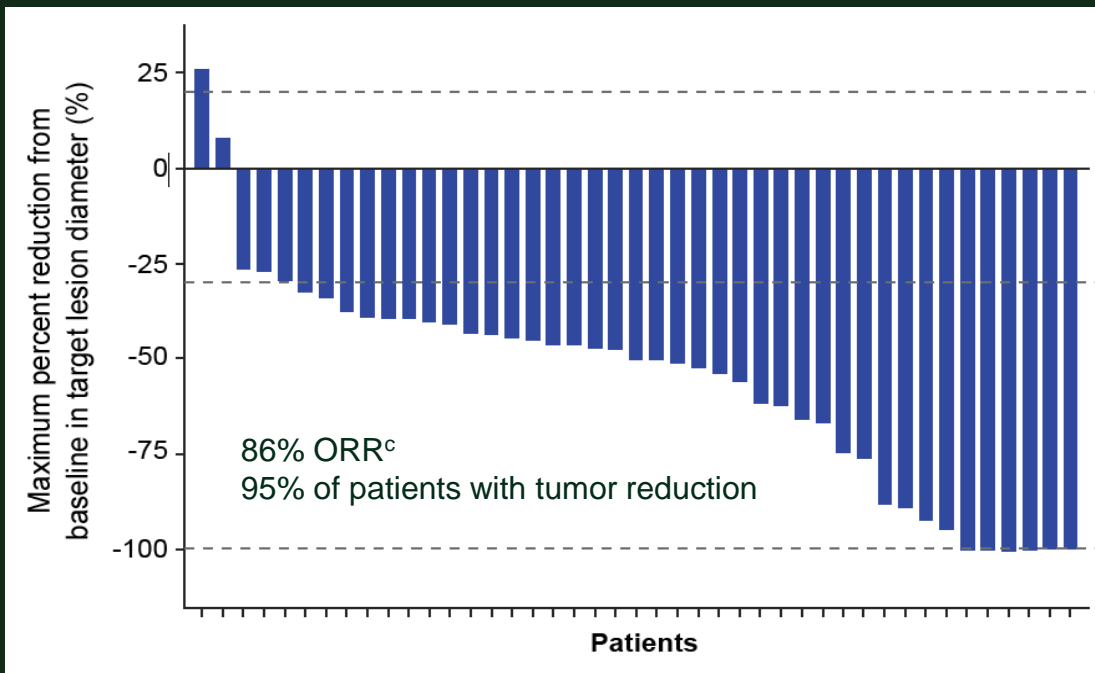
Most Common AEs Occurring in ≥ 15% of Patients, % (n)	300/400 mg QD Starting Dose (N = 204)			
	All AEs		Treatment-related AEs	
	All Grades ^b	Grade ≥3 ^c	All Grades ^b	Grade ≥3 ^c
Nausea	64.2 (131)	2.5 (5)	59.3 (121)	-
Fatigue	55.4 (113)	7.4 (15)	47.1 (96)	6.4 (13)
Anemia	50.0 (102)	28.4 (58)	36.3 (74)	16.2 (33)
Cognitive effects ^a	41.2 (84)	3.9 (8)	41.2 (84)	3.9 (8)
Periorbital edema	40.7 (83)	-	40.2 (82)	-
Vomiting	38.2 (78)	2.0 (4)	31.9 (65)	-
Decreased appetite	37.7 (77)	2.9 (6)	28.4 (58)	-
Diarrhea	37.3 (76)	4.9 (10)	31.9 (65)	2.9 (6)
Increased lacrimation	32.8 (67)	-	30.4 (62)	-
Peripheral edema	30.9 (63)	-	27.0 (55)	-
Face edema	24.5 (50)	-	24.0 (49)	-
Constipation	22.5 (46)	-	-	-
Dizziness	22.1 (45)	-	-	-
Hair color changes	21.1 (43)	-	20.6 (42)	-
Blood bilirubin increased	21.1 (43)	4.4 (9)	18.6 (38)	3.9 (8)
Abdominal pain	20.1 (41)	5.4 (11)	-	-
Headache	16.7 (34)	-	-	-
Dyspnea	16.7 (34)	2.5 (5)	-	-
Dyspepsia	15.7 (32)	-	-	-
Hypokalemia	15.7 (32)	2.9 (6)	-	-
Dysgeusia	15.2 (31)	-	15.2 (31)	-

- Most AEs were grade 1 or 2, with a higher incidence of commonly reported AEs in the 400 mg QD dose group compared with the 300 mg QD dose group
- No treatment-related grade 5 AEs were reported
- Most patients were able to remain on treatment with dose modifications when needed; relative dose intensity was 86% at 300 mg QD and 73% at 400 mg QD
- 8.3% of patients discontinued avapritinib for a treatment-related toxicity in the starting dose 300/400 mg QD group
 - 2.0% discontinued treatment for cognitive effects

^aCognitive effects include pooled terms of memory impairment (29.4%), cognitive disorder (10.8%), confusional state (7.4%), and encephalopathy (1.5%). Blueprint Medicines considered all cognitive effect AEs as treatment-related in this analysis. Note: 3 events of intracranial hemorrhage occurred; 2 were grade 3, 1 was grade 1. ^bAll grades AEs occurring in ≥15% of patients. ^cGrade ≥3 AEs occurring in ≥2% of patients. AE, adverse event; QD, once daily.



Antitumor Activity (Central Radiology Review): PDGFRA Exon 18 Avapritinib 300/400 mg QD Starting Dose



Best Response, ^a n	PDGFRA Exon 18 n=43
CR	3
PR ^b	34 (1 pending)
SD	5
PD	1
ORR (CR+PR), ^c % (95% CI)	86.0 (72.1–94.7)
CBR, ^d % (95% CI)	95.3 (84.2–99.4)
DOR, ^e months (95% CI)	NE (11.5–NE)
PFS, months (95% CI)	NE (13.4–NE)

^aAssessed by mRECIST 1.1. Patients who have had ≥ 1 post-baseline radiographic assessment. Response-evaluable at 300/400 mg QD. ^b1 response pending confirmation. ^cORR defined as the proportion of patients with a confirmed best response of CR or PR. ^dCBR defined as CR/PR+SD lasting ≥ 16 weeks from first dose. ^eDOR defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever came first. CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease.

Best Confirmed Response PDGFRA Exon 18 by Line of Therapy

Best Response, % (n)	300/400 mg QD Starting Dose		
	1L n=5	2L+ n=38	Total n=43
CR	40.0 (2)	2.6 (1)	7.0 (3)
PR	60.0 (3)	78.9 (30)	76.7 (33)
SD	0	15.8 (6)	14.0 (6)
PD	0	2.6 (1)	2.3 (1)

- Avapritinib demonstrated efficacy in first line and subsequent lines of therapy in the PDGFRA Exon 18 population

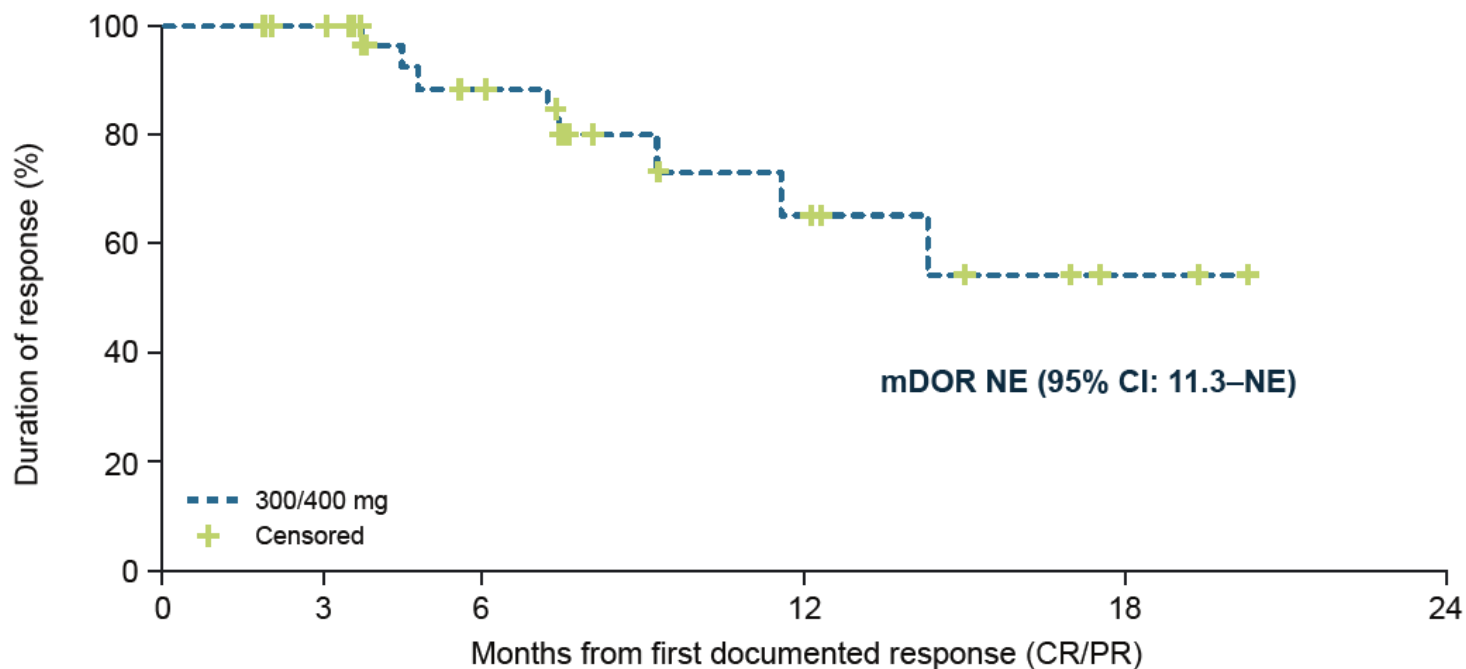
25

1L, 1st treatment line; 2L+, 2nd or later treatment line; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.



Duration of Response

PDGFRA Exon 18 Avapritinib 300/400 mg QD



Number at risk
300/400 mg QD:*

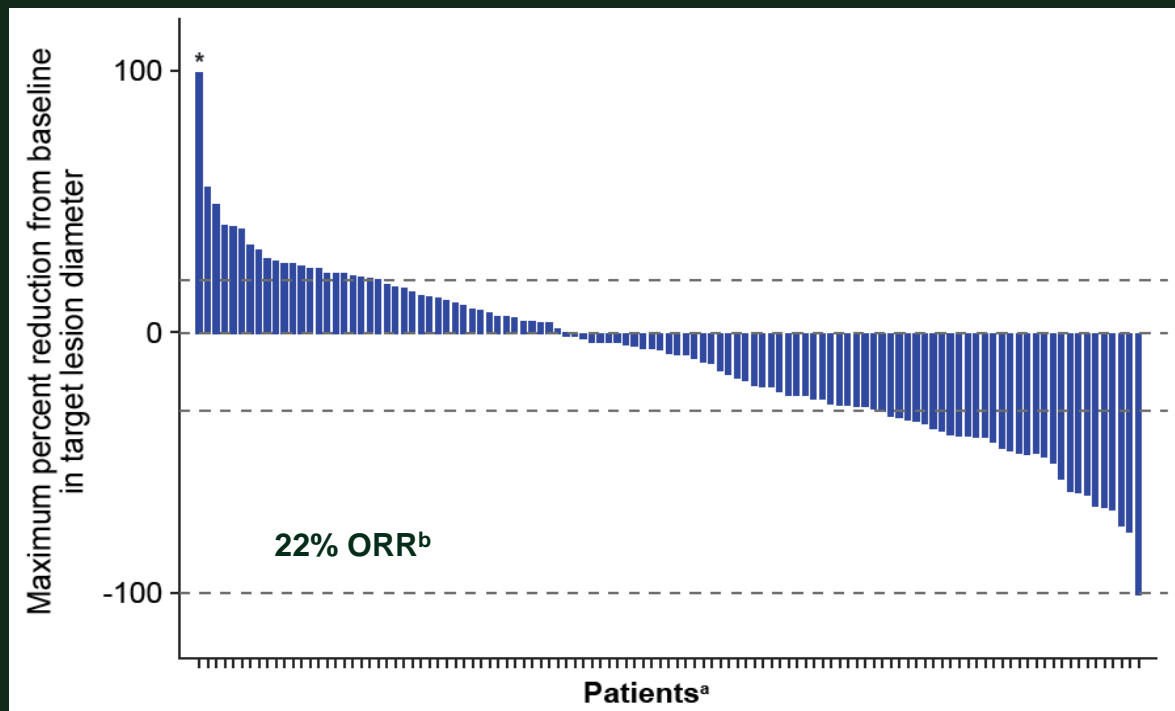
36 33 22 8 2 0

- 78% (28/36) of PDGFRA Exon 18 patients were still in response as of the November 16, 2018, data cutoff
- Median follow-up was 10.9 months

*Patients with confirmed response. DOR was defined as the time from first documented response (CR/PR) to the date of the first documented disease progression or death due to any cause, whichever came first. Patients without confirmed CR/PR were excluded from this analysis. CI, confidence interval; CR, complete response; mDOR, median duration of response; NE, not evaluable; NR, not reached; PDGFRA, platelet-derived growth factor receptor alpha; PR, partial response; QD, once daily.



Antitumor Activity (Central Radiology Review) 4L+ Avapritinib 300/400 mg QD Starting Dose



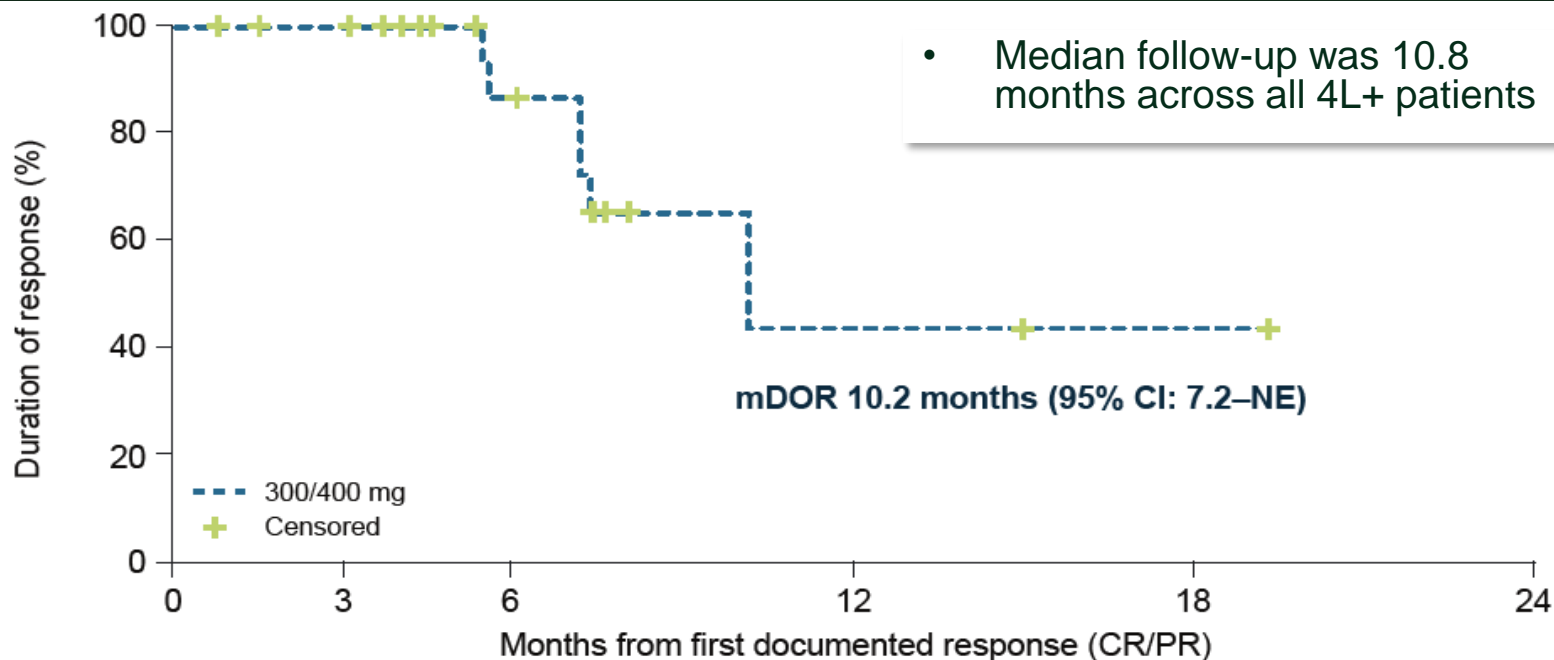
Best Response ^c , n	4L+ N=111
CR	1
PR (confirmed)	23 (1 pending)
SD	52
PD	35
ORR (CR+PR), % (95% CI)	22 (14.4–30.4)
CBR, % (95% CI)	41 (32.2–51.2)
DOR, months (95% CI)	10.2 (7.2–NE)
PFS, months (95% CI)	3.7 (3.4–5.6)

[†]One patient had an outlier value for percent change from baseline of >200% increase in target lesion diameter. ^aTwo patients who had best response assessment are not included in the waterfall plot because they did not have measurable target lesions at baseline and thus, no percent change could be calculated. ^bThere were 8 patients with PDGFRA D842V mutations and when these patients were removed from analysis, the ORR was 17% and DOR remained unchanged. ^cAssessed by mRECIST 1.1. Patients who have had ≥ 1 post-baseline radiographic assessment. Response-evaluable at 300/400 mg QD. CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; mRECIST, modified Response Evaluation Criteria in Solid Tumors; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once daily; SD, stable disease.



Duration of Response

4L+ Avapritinib 300/400 mg QD Starting Dose



Number at risk
300/400 mg QD:*

23

21

13

2

1

0

*Patients with confirmed response. DOR was defined as the time from first documented response (CR/PR) to the date of the first documented disease progression or death due to any cause, whichever came first. Patients without confirmed CR/PR were excluded from this analysis. 4L, 4th line; CI, confidence interval; CR, complete response; mDOR, median duration of response; NE, not evaluable; PR, partial response. A DOR was defined as the time from first documented response (CR/PR) to the date of first documented disease progression or death due to any cause, whichever came first. Patients without confirmed CR or PR were excluded from this analysis. Patients who were still in response at time of data cutoff were censored at their last valid assessment.

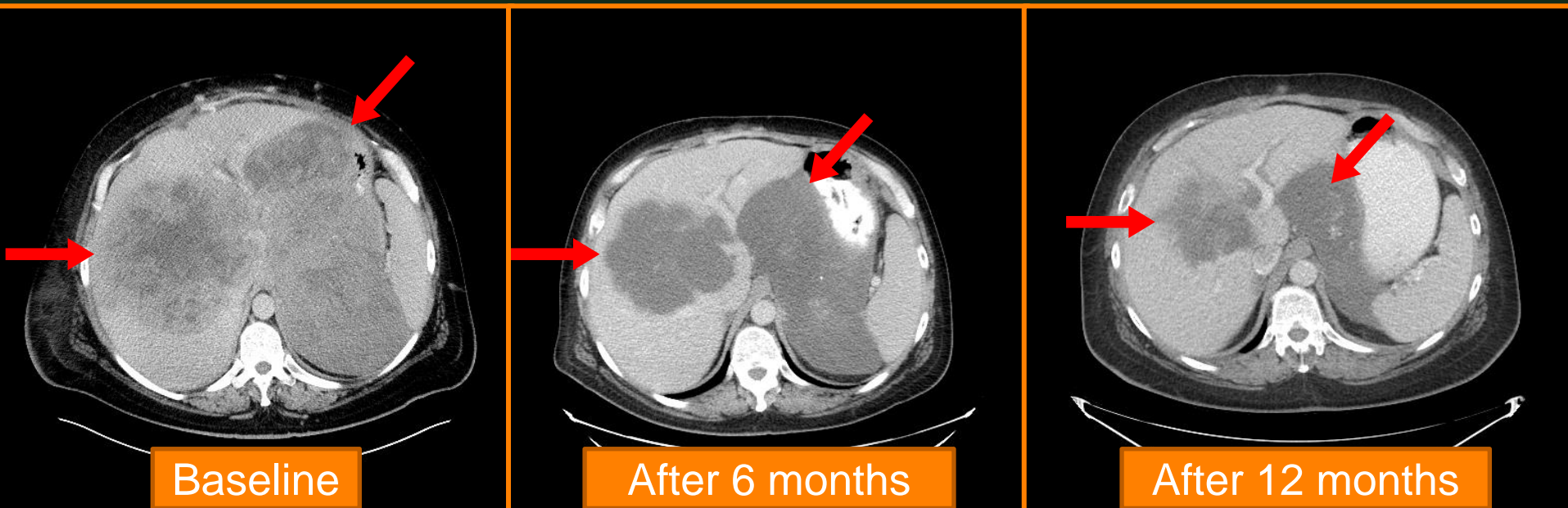


CONCLUSIONS

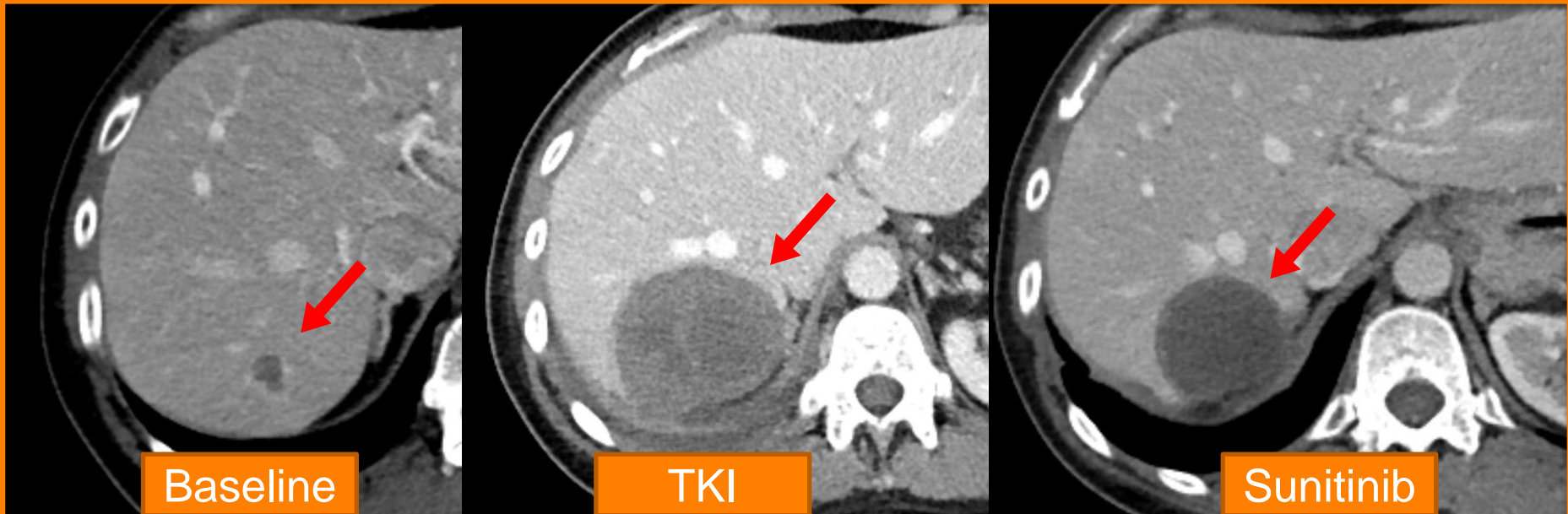
- Pivotal data analyses from the NAVIGATOR trial demonstrate important clinical activity and favorable tolerability in advanced Exon 18 mutant PDGFRA and 4L+ GIST, highlighting the potential of avapritinib to change the treatment paradigm for patients with advanced GIST
 - Avapritinib shows **remarkable activity in both D842V**, a previously undruggable target, and other Exon 18 mutant PDGFRA GIST
 - In the fourth line setting, patients with advanced GIST have no effective therapies; **avapritinib has activity with durable responses**, and response rates exceeding that reported with other kinase inhibitors
 - The **safety profile of avapritinib is predictable and manageable**, thus allowing for prolonged treatment in patients benefiting from avapritinib
 - Based on its overall safety profile and antitumor activity, avapritinib 300 mg QD is the recommended dose for patients with unresectable or metastatic GIST



- 55 YO man with Gastric, **KIT exon 11 (W557-K558del)** mutant, GIST with liver metastases
- Progressive on imatinib, nilotinib, sunitinib, regorafenib.
- ctDNA revealed **KIT exon 17 Y823D** resistance mutation
- Placed on **Ponatinib** to target *KIT* exon 17



- 52 YO woman with small intestine, **KIT exon 11 (L576P)** mutant, GIST with liver metastases
- Progressive on imatinib placed on **TKI**, rapid progression
- ctDNA revealed **KIT exon 13 V654A** resistance mutation
- Placed on **Sunitinib** to target *KIT* exon 13



Conclusion

- **Primary and resistance mutations should be determined in order to provide optimal therapy for GIST patients.**
- Liquid biopsy, ctDNA, is a rapid, non-invasive tool to detect mutations
- Avapritinib and ripretinib are new active agents for GIST patients.
- Earlier lines of therapy?
- Neoadjuvant or Adjuvant?
- Combinations?



Sylvester Comprehensive Cancer Center

GIST/Sarcoma Team

- **Medical Oncology**
 - Jon Trent
 - Gina D'Amato
 - Emily Jonczak
 - Aditi Dhir (ped)
- **Pathology**
 - Andrew Rosenberg
 - Elizabeth Montgomery
 - Daniel Cassidy
 - Jay-Lou Torres
- **Radiology**
 - Ty Subhawong
 - Jean Jose
- **Nurse Practitioner**
 - Morgan Smith
 - Solange Sierra
 - Yolanda Roper
- **Nursing**
 - Eryka Lacayo
 - Vilma Sanchez
 - Lila Wong
- **Trainees**
 - Andrea Espejo
 - Priscella Coelho
 - Phillipos Costa
- **Orthopedic Oncology**
 - Sheila Conway
 - Frank Eismont
 - Juan Pretell
 - Mo Al Maaieh
- **Surgical Oncology**
 - Nipun Merchant
 - Alan Livingstone
 - Neha Goel
 - Dido Franceschi
- **Radiation Therapy**
 - Raphael Yechieli
 - Aaron Wolfson
- **Head & Neck Surgery**
 - Zoukaa Sargi
 - Frank Civantos
- **Thoracic Surgery**
 - Dao Nguyen
 - Nestor Villamizar
- **Interventional Radiology**
 - Shree Venkat
 - Prasoon Mohan
- **Gynecologic Oncology**
 - Matt Schlumbrecht
 - Marilyn Huang
 - Abed Sinno
- **Clinical Research**
 - Yvonne Nunez
 - Melissa Serna
 - Mirna Gonzalez
- **Lab Research**
 - Joanna DeSalvo
 - Luyuan Li, PhD
 - Karina Galoian
 - Josie Eid, PhD
- **Social Work**
 - Marlene Morales
 - Abby Solomon



New Horizons 2020

New Agents for GIST Patients

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