

New Horizons GIST- Special Topic:

Mutational Analysis in GIST as a guide for the right therapy...

Clinical Impact of GIST Mutational Testing

Rashmi Chugh, MD

Professor of Internal Medicine

Connective Tissue Clinical Research Program Co-Lead

University of Michigan Rogel Cancer Center



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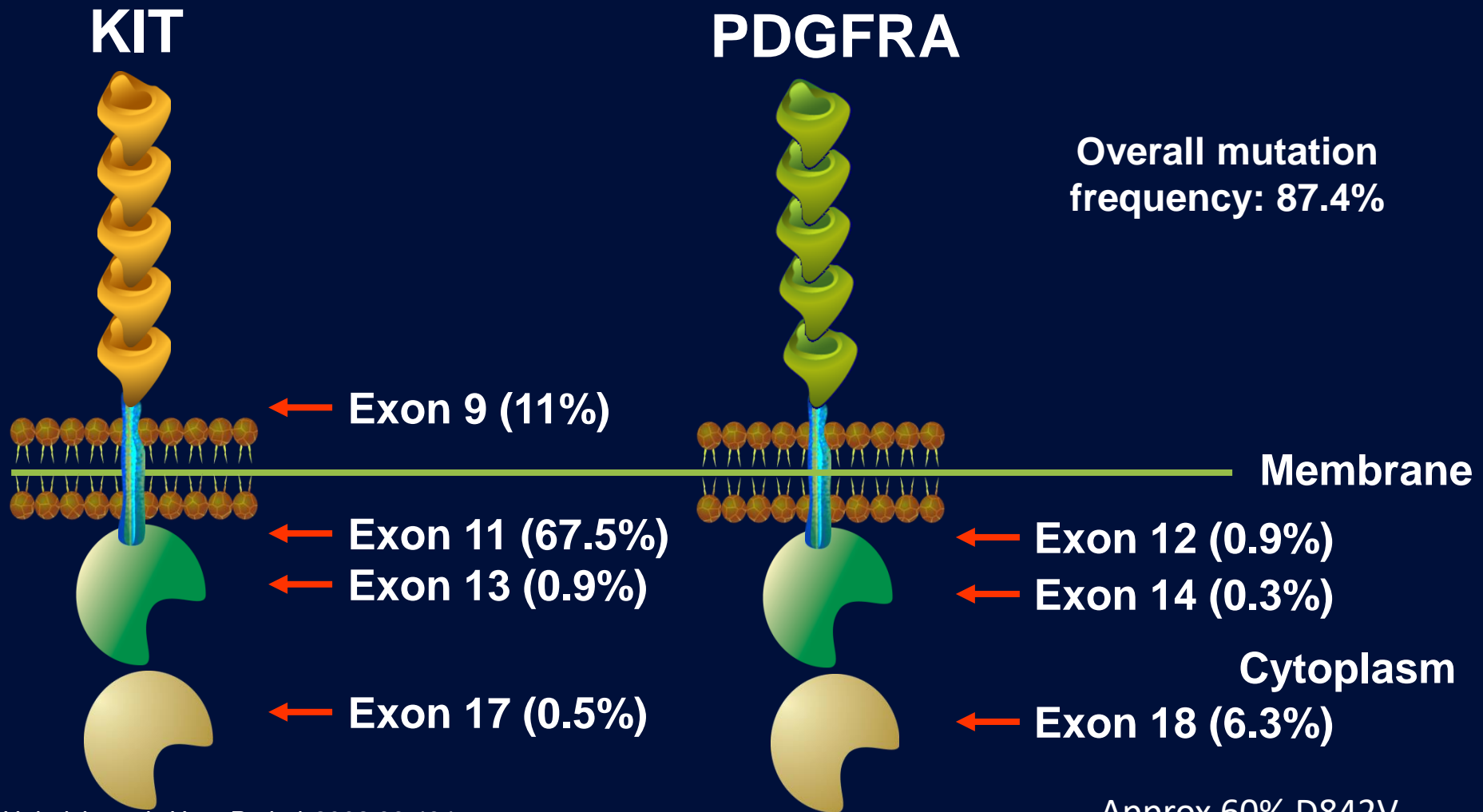
Learning Objectives:

- Activity of different drugs in different GIST mutations
- Primary mutations as a guide for choice of therapy
- Secondary mutations as a guide for choice of therapy
- Options for specific, very rare mutations

Major Agents in GIST- Tyrosine Kinase Inhibitors

- Imatinib- Approved FDA/EMA (2001)
 - metastatic, adjuvant setting
- Sunitinib-Approved FDA/EMA (2006)
 - post-imatinib failure/intolerance
- Regorafenib-Approved FDA/EMA (2013)
 - post imatinib/sunitinib failure/intolerance
- Avapritinib -Approved FDA/EMA (2020)
 - GISTs harboring PDGFRA exon 18 mutation, including D842V mutations
- Ripretinib- Approved FDA (2020), Evaluating EMA (Q3 2021?)
 - After 3 or more prior TKIs including imatinib

Most Common Primary GIST mutations: KIT and PDGFRA Mutations

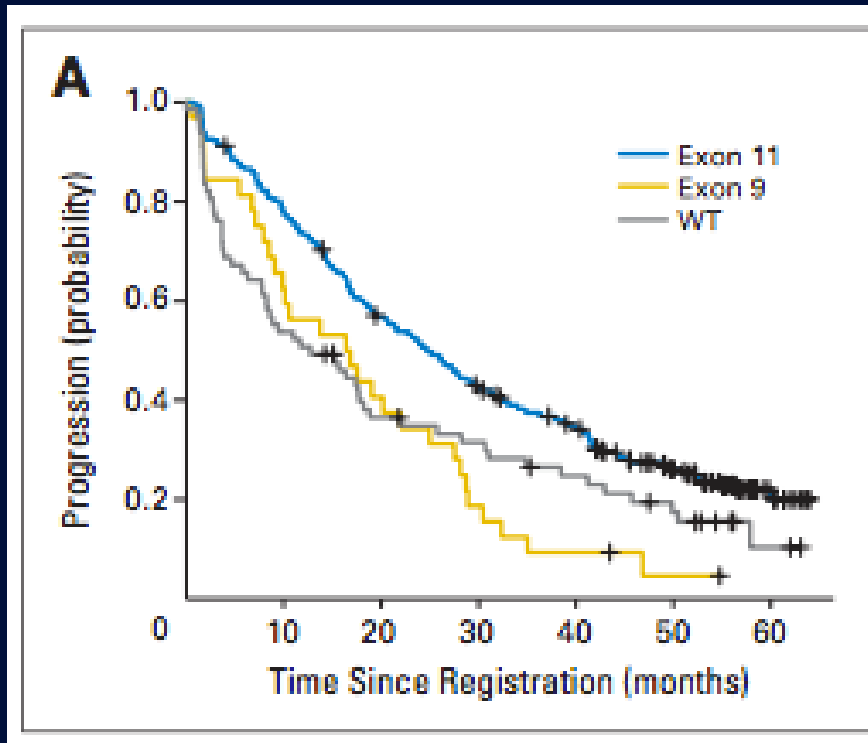


Heinrich et al. *Hum Pathol.* 2002;33:484.
Corless et al. *Proc Am Assoc Cancer Res.* 2003;44. Abstract R4447.

Approx 60% D842V

Imatinib activity based on GIST Mutation

CALGB150105/SWOG S0033 study of 428 patients with advanced GIST with mutation information treated with imatinib 400mg or 800 mg daily



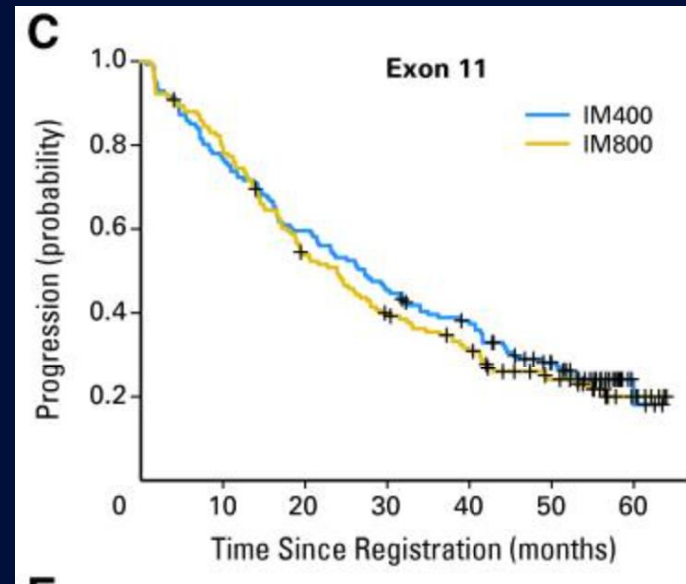
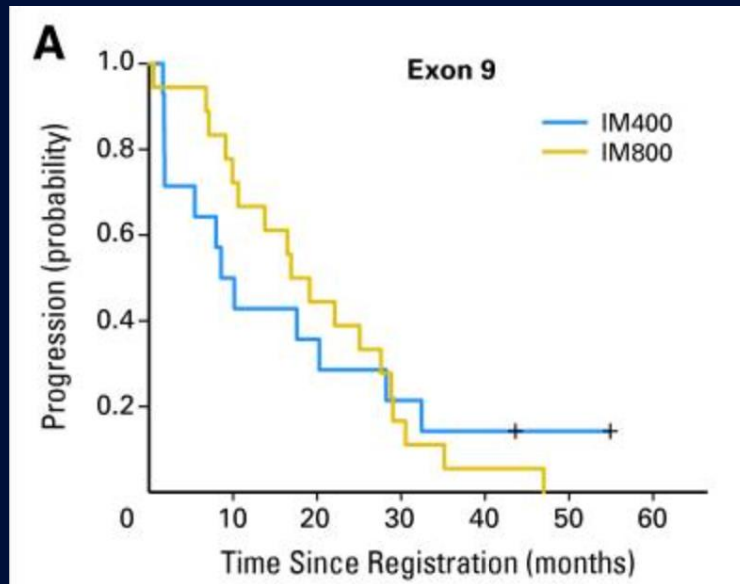
Response Rates by mutation status:

- Exon 11: 71.7%
- Exon 9: 44.4%
- Wild-Type: 44.6%

→ GISTs with KIT exon 11 mutations are controlled for longer with imatinib as compared to GISTs with KIT exon 9 mutations and Wild type

GIST response to escalating imatinib dose by genotype

CALGB150105/SWOG S0033 study comparing dose of imatinib of 400 mg or 800 mg in patients with advanced GIST with mutation information



Response Rates in patients with Exon 9 mutated GISTs by dose of imatinib

- 800 mg: 67%
- 400 mg: 17%

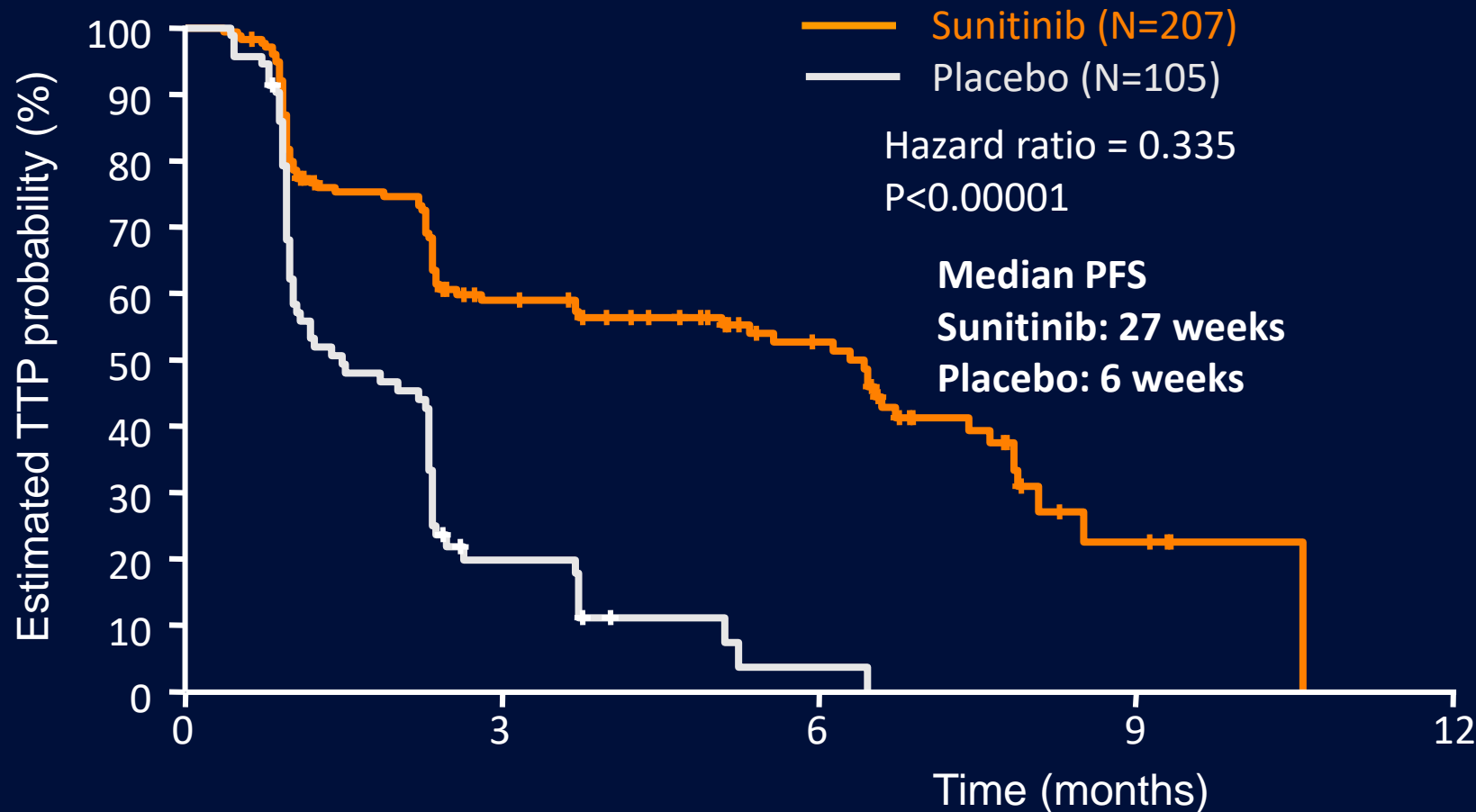
→ Exon 9 mutant GISTs more likely to be controlled with higher dose imatinib

Similar findings in MetaGIST study combining data with EORTC/Italian/Australian trial 62005

JCO 2010, 28:1247-1253.

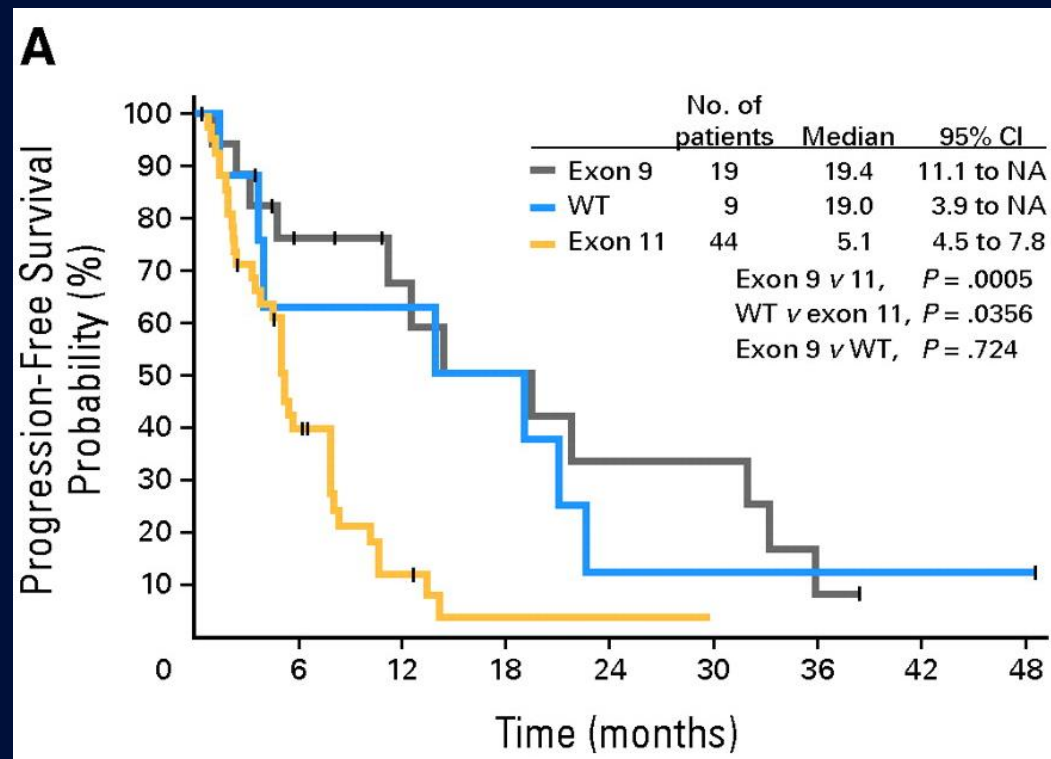
Heinrich et al. JCO 2008 26:5360-5367.

Phase 3 study of imatinib-resistant GIST treated with Sunitinib vs placebo



- 312 pts randomized 2:1 to sunitinib versus placebo
- Sunitinib 50mg daily 4 weeks on, 2 weeks off

Sunitinib activity based on GIST Mutation

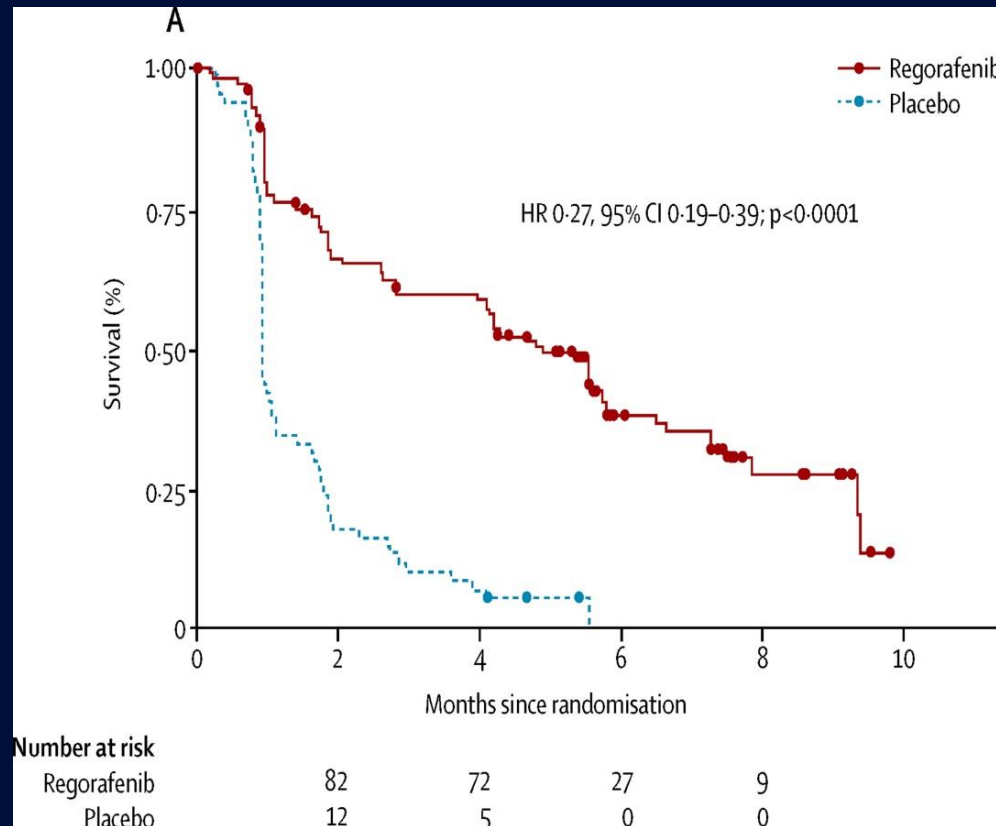


→ Patients with GISTS with KIT exon 9 mutations and Wild type were controlled for longer with sunitinib as compared to KIT exon 11 mutations

→ Sunitinib can also have activity in GISTS with KIT exon 13/14 mutations

Similar findings in worldwide treatment-use study evaluating 230 patients treated with sunitinib with mutational information

Phase 3 study of imatinib, sunitinib-resistant GIST treated with Regorafenib vs placebo (GRID)



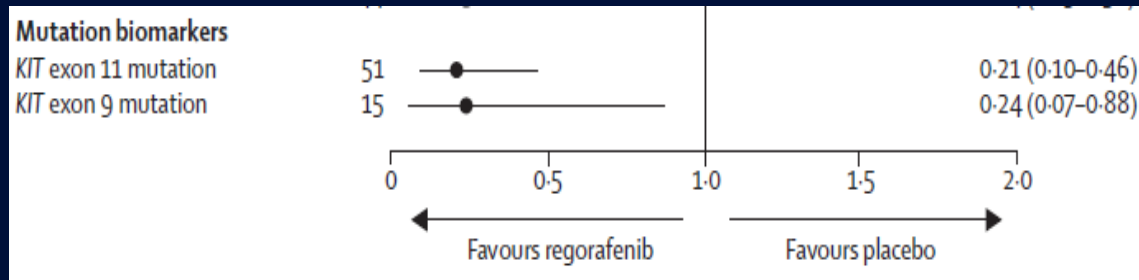
- 199 pts randomized 2:1 to regorafenib versus placebo
- Regorafenib 160mg daily 3 weeks on, 1 week off

Median PFS

Regorafenib: 4.8 months

Placebo: 0.9 months

Regorafenib activity based on GIST Mutation

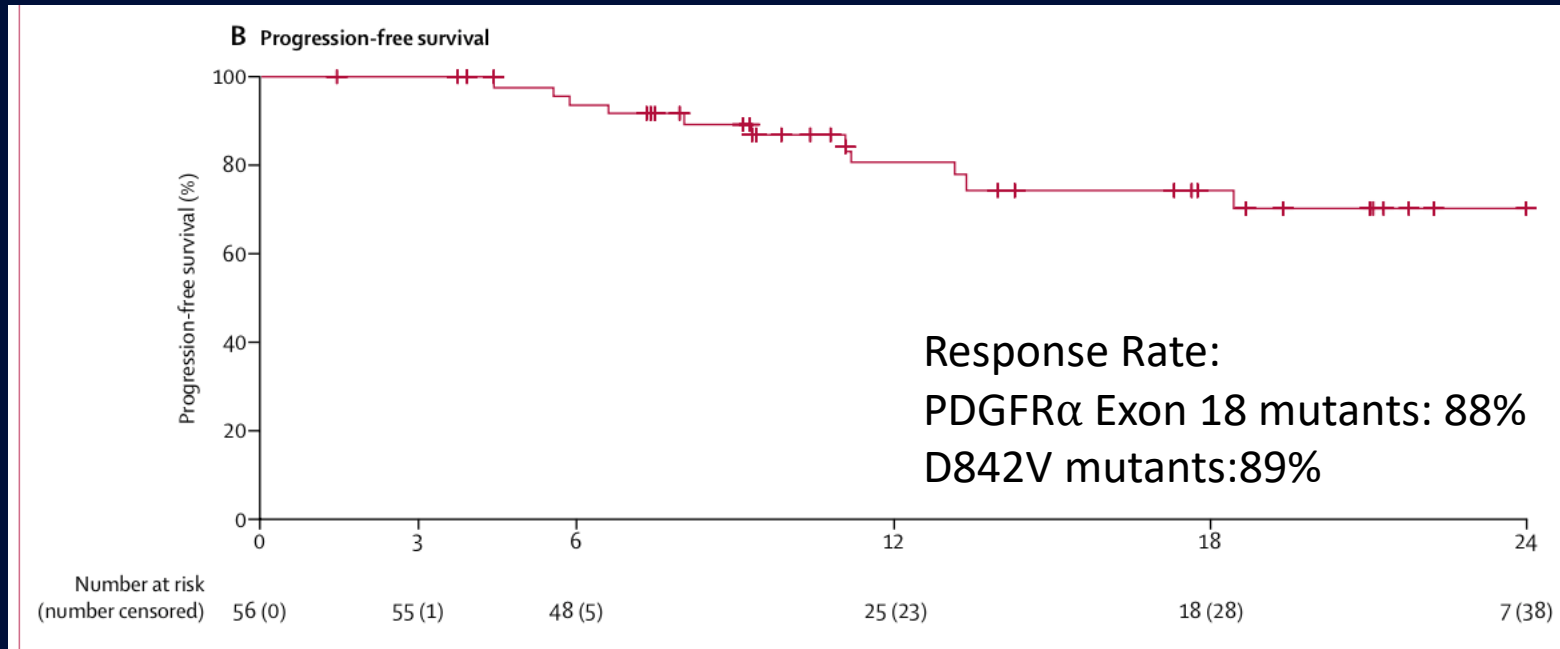


→ GISTs with both KIT exon 11 and exon 9 mutations were controlled with regorafenib

→ Regorafenib can also have activity in GISTs with KIT exon 17 mutations



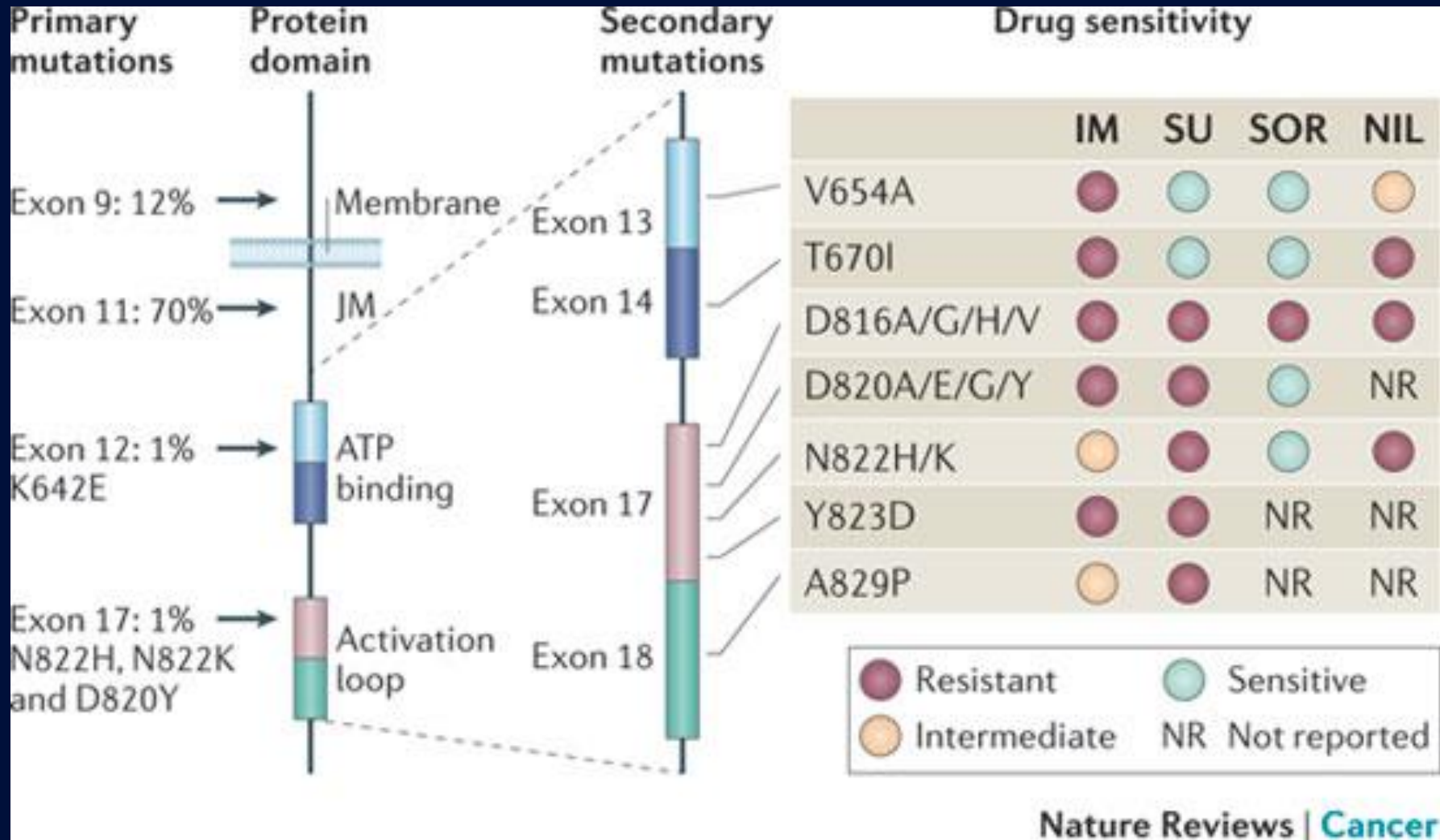
Avapritinib in advanced PDGFRA -mutant GIST: multicenter, phase 1 trial



→ Patients with GIST with PDGFR α mutations in exon 18 treated with avapritinib experienced clear benefit. Notably in typically resistant D842V mutants.

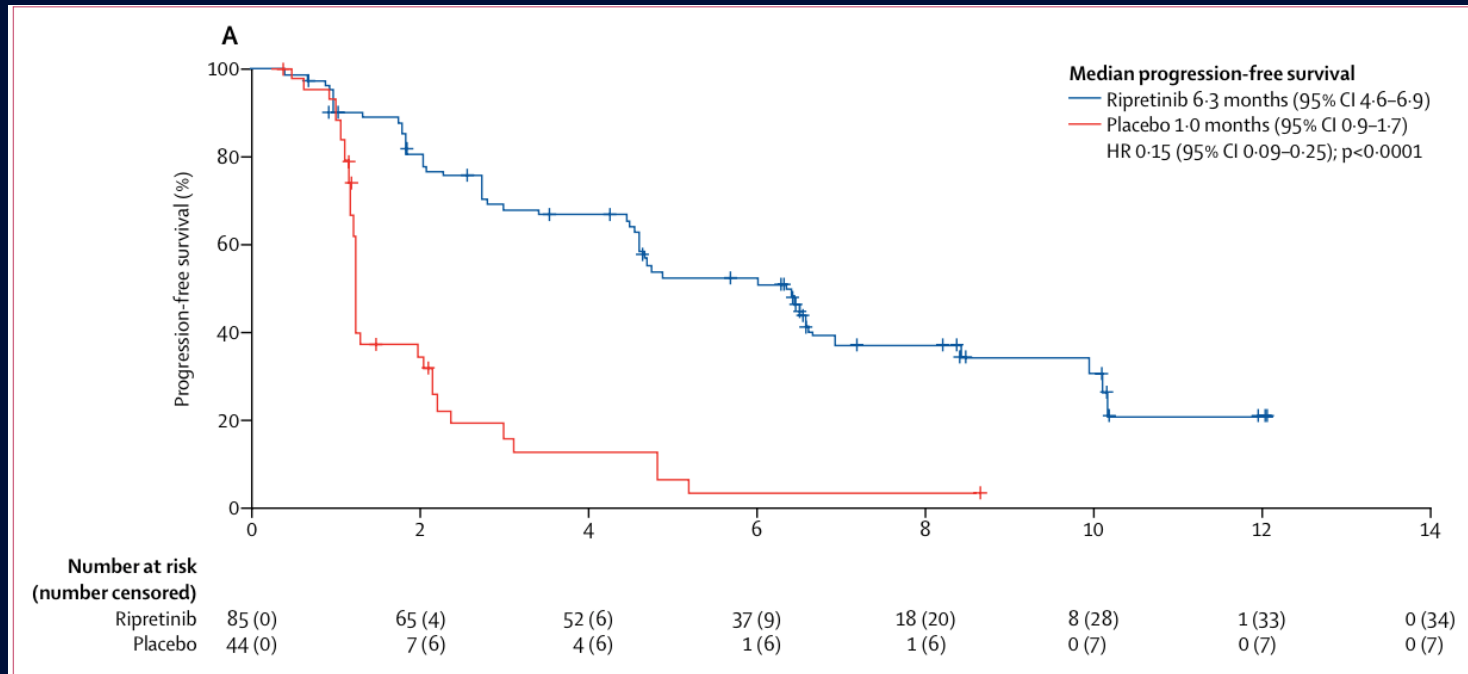
Avapritinib shown to be very selective in blocking KIT and PDGFRA in the active state which is found in GIST with PDGFR α D842V mutants

Secondary mutations in KIT



Corless CL et al, 2011, Nature Reviews Cancer 11:868-878

Phase 3 study of Ripretinib vs placebo in advanced GIST (INVICTUS)

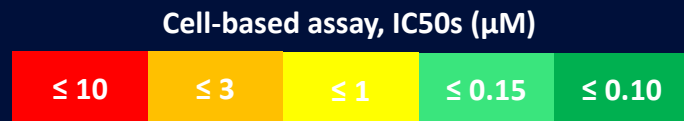


→ Patients with GIST with multiple mutations treated with ripretinib experienced benefit over placebo after developing resistance to at least 3 other drugs.

Switch Control tyrosine kinase inhibitor which binds two areas to broadly block multiple mutations

Conformation-Specific Inhibitors Have Complementary Profiles Against Secondary KIT Mutations

	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
Avapritinib	Green	Green	Green	Red	Yellow	Green	Green
Ripretinib	Green	Green	Green	Yellow	Green	Green	Green
PLX9486 + Sunitinib	Green	Green	Green	Green	Green	Green	Green



Primary GIST Mutations: Initial Management strategies

Mutation	Management
KIT Exon 11	Imatinib 400 mg daily
KIT Exon 9	Imatinib 400 mg daily (escalate to 800 mg as tolerated)
PDGFR α Exon 18 (D842V) *	Avapritinib
PDGFR α Exon 18 (non-D842V)	Imatinib
PDGFR α non-Exon 18	Imatinib
SDH deficiency *	VEGFR-directed therapies Sunitinib/Regorafenib
KIT Exon 13	Imatinib

**Primary
mutation status
must useful to
recognize
Imatinib
Resistance***

Very RARE GIST Mutations*: Management strategies

Mutation	Management
TRK Fusion	TRK inhibitors
NF-1 associated	MEK inhibitors (?)
BRAF V600E	BRAF + MEK inhibitors (?) Regorafenib
FGFR alterations	FGFR inhibitors
RAS/RAF alterations	RAF/MEK inhibitors
IGF1R amplified	IGFR1R -directed therapies

**Clinical Trials
Optimal
Strategy for
Rare
Mutations!!!**

Typically Imatinib Resistant*

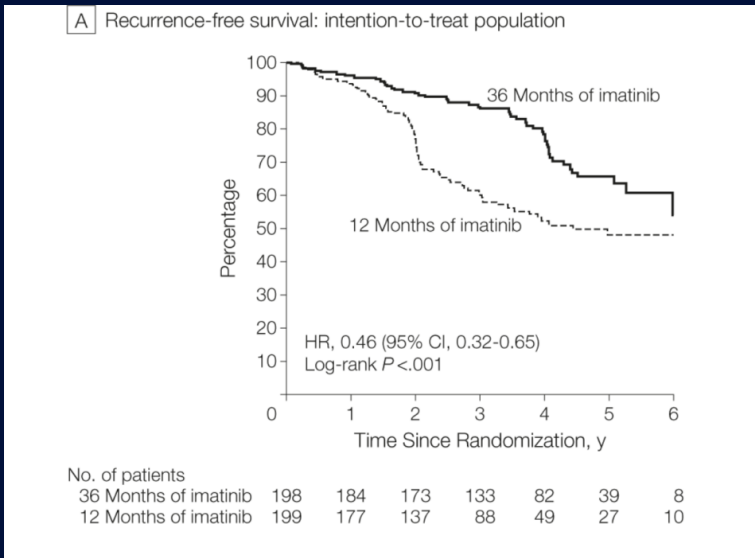
Secondary GIST Mutations: Management strategies

Mutation	Management
KIT Exon 13/14 (ATP Binding domain)	Sunitinib
KIT Exon 17/18 (Activation loop)	Regorafenib Ripretinib

**Clinical Trials
Ongoing to
address
resistance=
Combinations,
New Agents**

What about mutations in Adjuvant Therapy?

SSG/AIO study of 1 year vs 3 years of adjuvant imatinib



5-yr Recurrence Free Survival rate

- 66% - 3 yrs imatinib
- 48% - 1 yr imatinib

GIST mutation

- 65% KIT exon 11
- 6% KIT exon 9
- 22% PDGFR (9% D842V)
- 9% wild-type

→ Only large experiences with imatinib as preventative drug
→ Not appropriate for imatinib-resistant mutations

Tumor mutation site	12-mo Group		36-mo Group		HR (95% CI)	Favors 36 mo of Imatinib	Favors 12 mo of Imatinib	P Value
	No. of patients	No. of patients	No. of patients	No. of patients				
KIT exon 9	12	14	8	8	0.61 (0.22-1.68)			.34
KIT exon 11	129	127	55	28	0.35 (0.22-0.56)			<.001
Wild type	19	14	9	3	0.41 (0.11-1.51)			.17
Other	28	23	6	4	0.78 (0.22-2.78)			.70

Summary: Mutational Analysis Guides Treatment!

- For most GIST patients, imatinib is still first choice
 - Exception is for Imatinib-resistant GIST
 - **PDGFR α D842V** mutant, **SDH deficient**, **Very rare mutants**
 - Consider initial dose escalation of imatinib with **Exon 9** mutants
- Subsequent therapies have activity across mutations
 - Exon 13 mutations- sunitinib
 - Exon 17-regorafenib/ripretinib
- Imatinib only treatment approved for preventative (adjuvant) therapy
 - Consider other agents if imatinib intolerant and mutation type.

Acknowledgments....

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Sarcoma colleagues internationally

Thank you! !

rashmim@med.umich.edu

