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)

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Background GIST demographics and treatment

- GIST is the **most common malignant neoplasm of mesenchymal origin**
  - Annual incidence of 10 – 15 cases / million / year
- Over 85% of GIST cases are driven by an activating mutation in ***KIT*** **(75%) or** ***PDGFRA*** **(10%)** → uncontrolled activation of kinase signaling
  - Wide variety of amino acid changes across well-defined exons
- **Tyrosine kinase inhibitors (TKIs) targeting KIT and PDGFRA** have dramatically improved clinical outcomes for patients with metastatic GIST
  - Median overall survival has improved **from <12 months to ~ 5 years**
- **Approved agents**: imatinib, sunitinib, regorafenib, ripretinib, avapritinib

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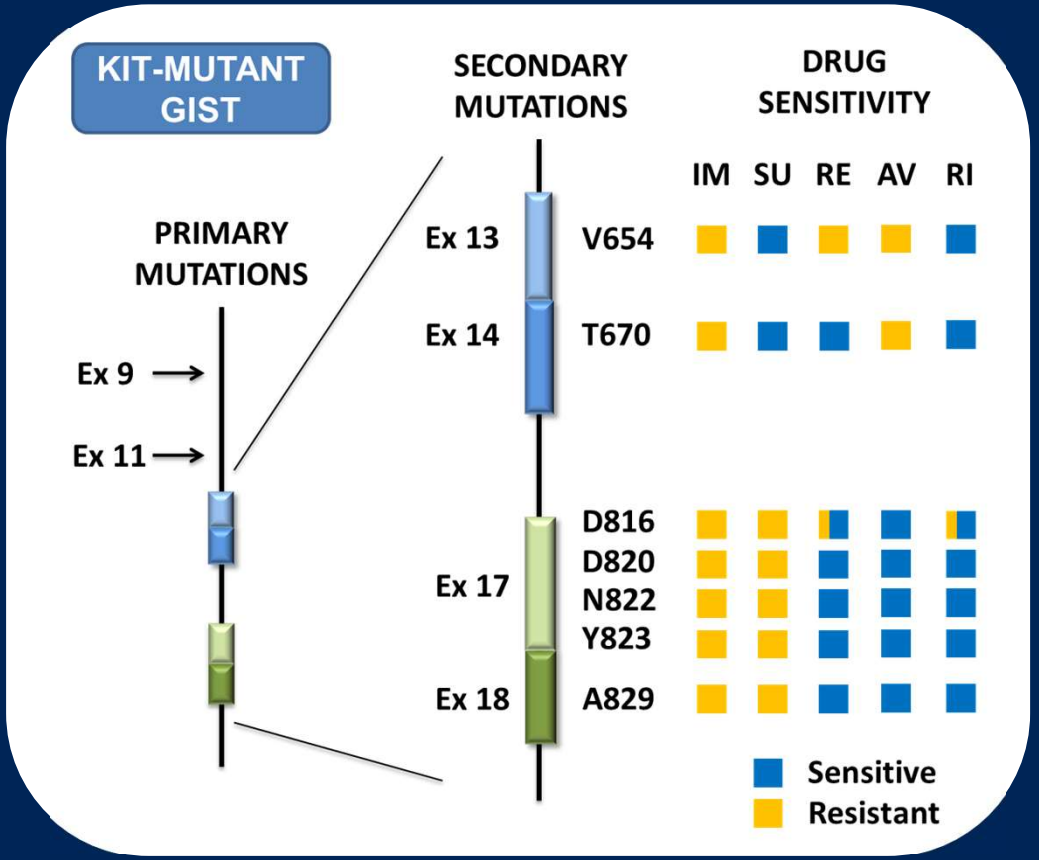
Background TKI-resistance is defined by KIT secondary mutations

- 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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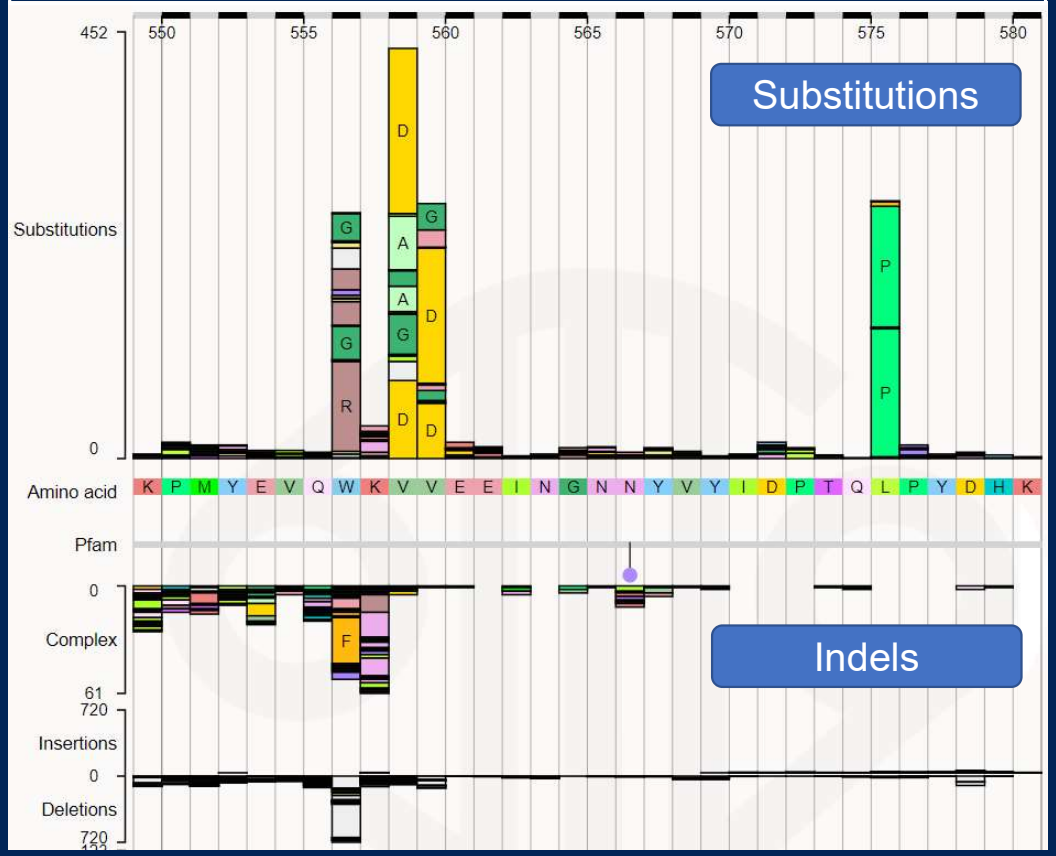
Background ctDNA in GIST

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

Genetic alterations affecting *KIT* exon 11



Data obtained from COSMIC

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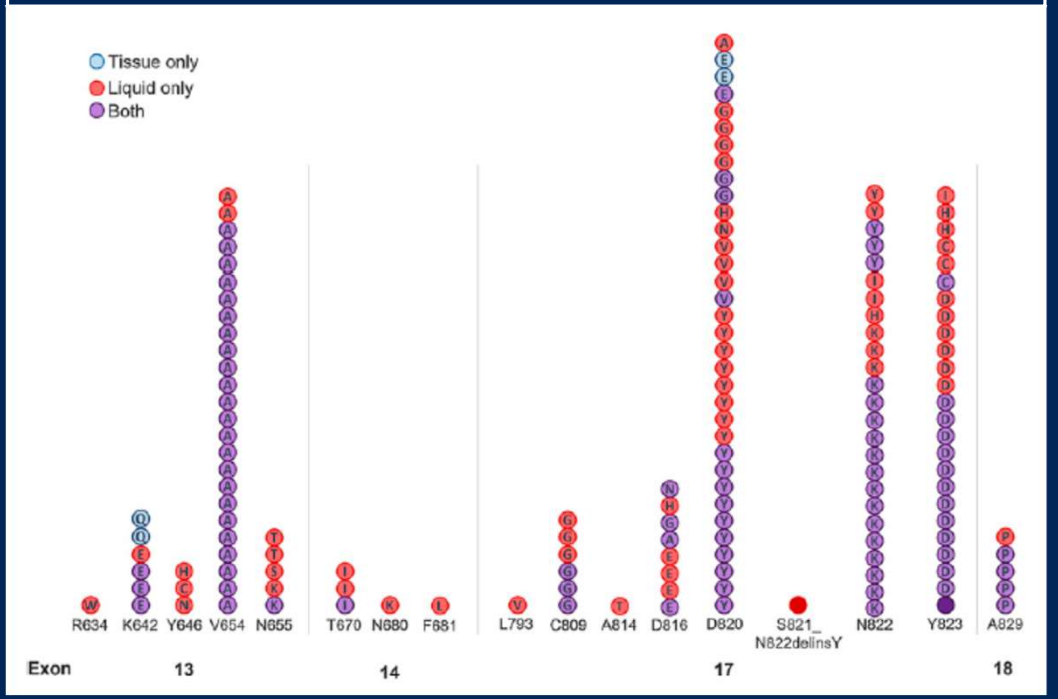
Background ctDNA in GIST

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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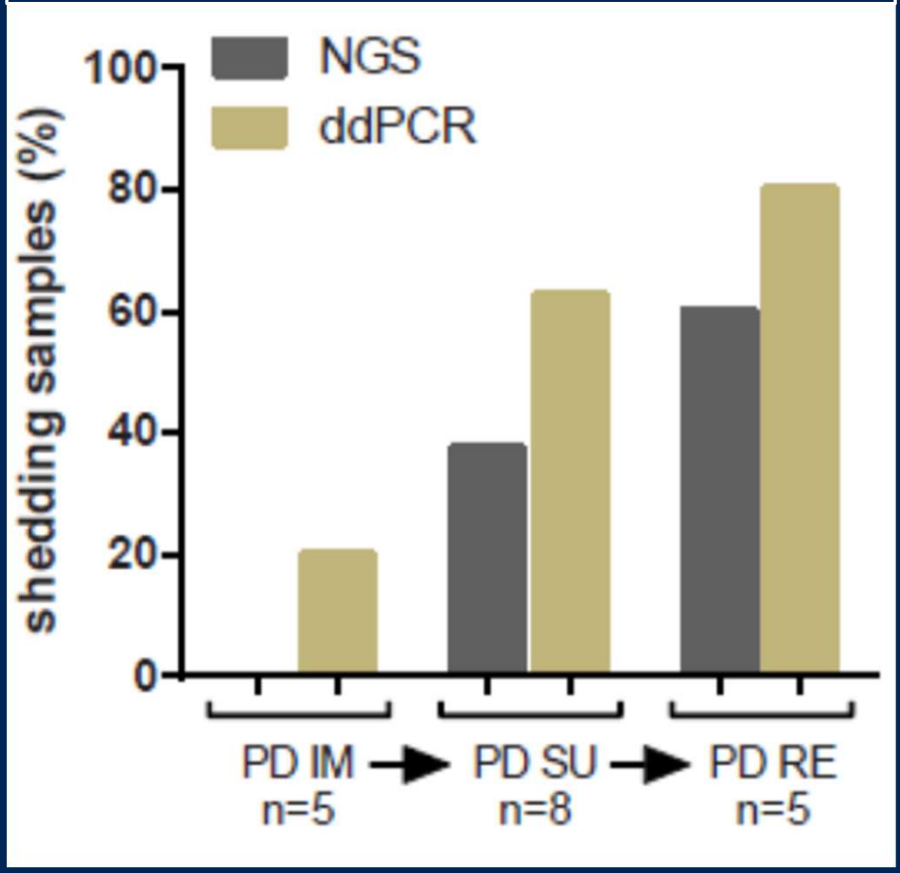
Background ctDNA in GIST

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

2. ↓ **ctDNA shedding** in GIST

ctDNA positive in late stages



Serrano C et al, *BMC Cancer* 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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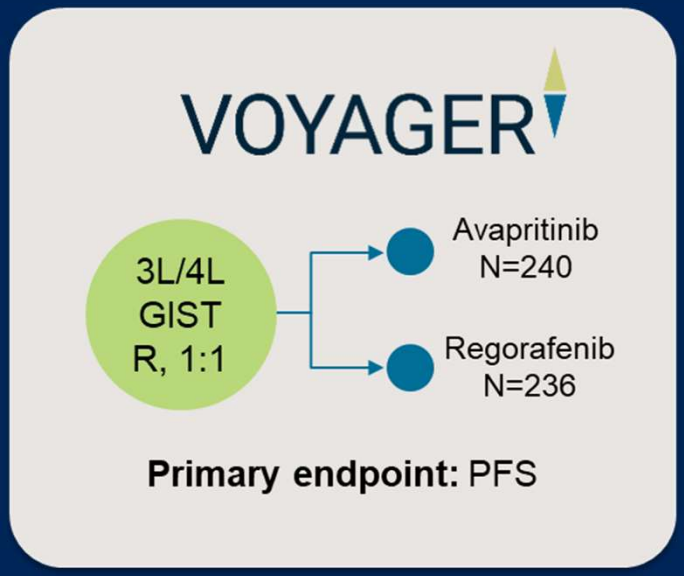
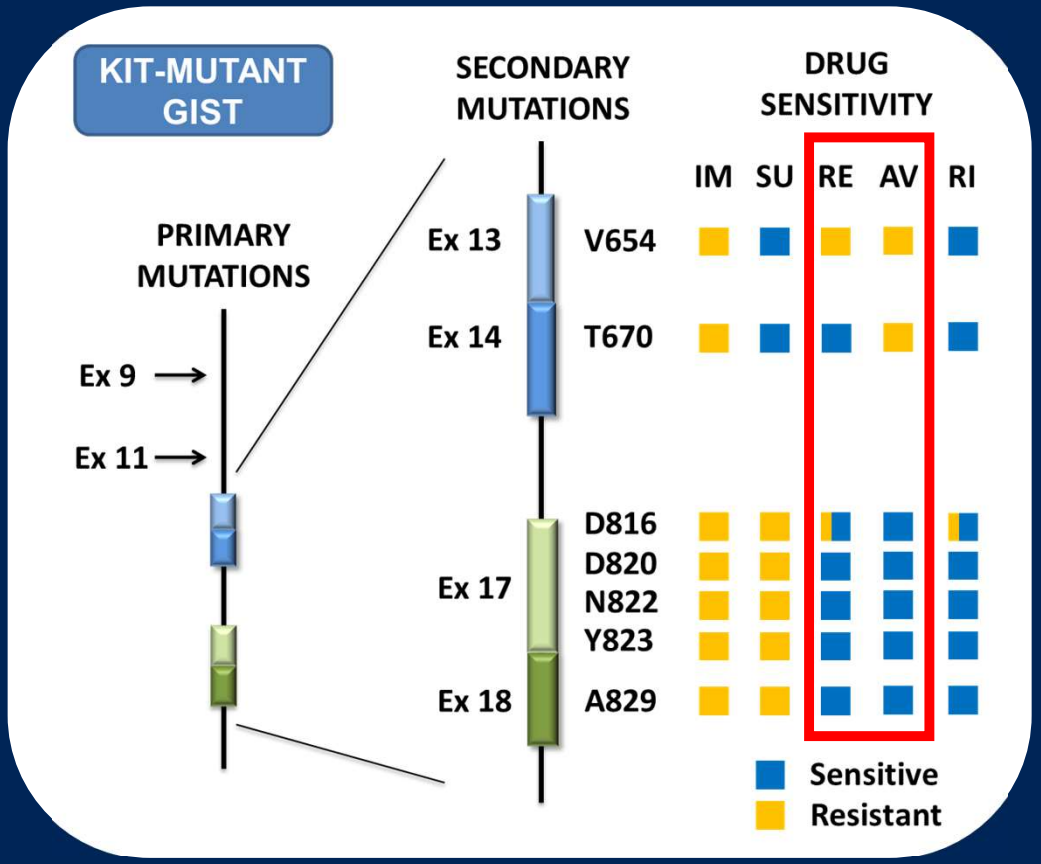
Background VOYAGER phase III clinical trial





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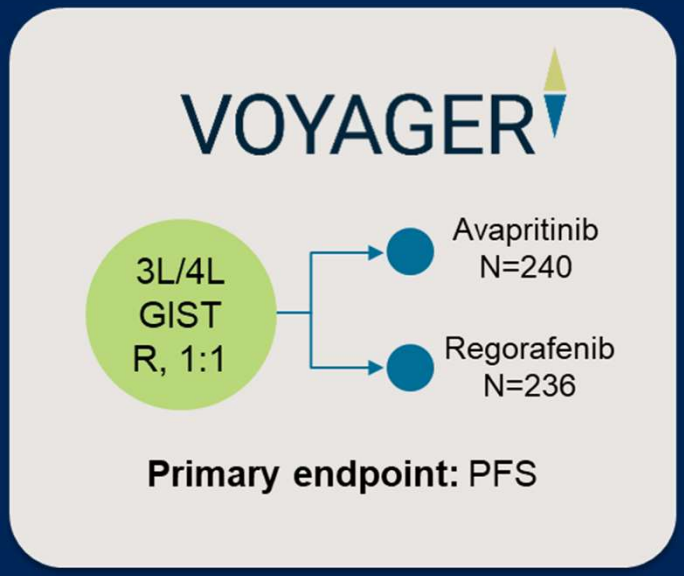

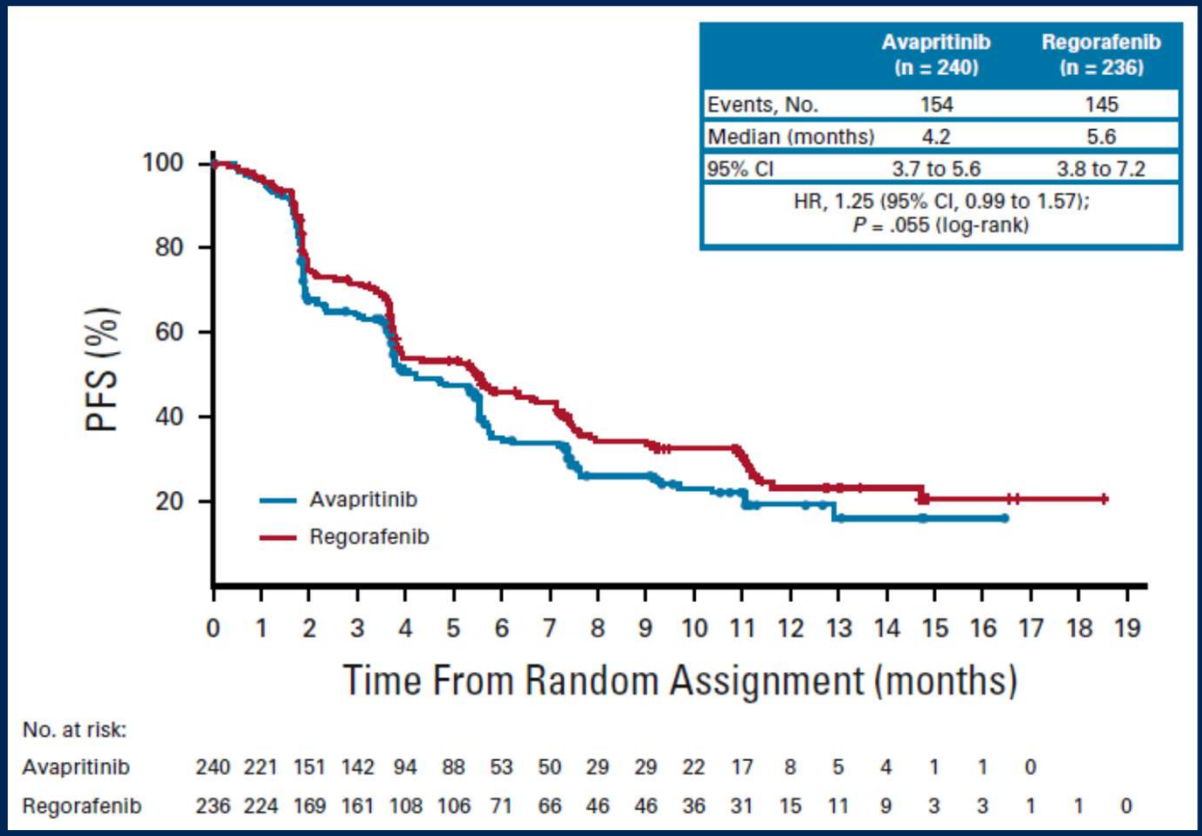

Kang YK et al, J Clin Oncol 2021

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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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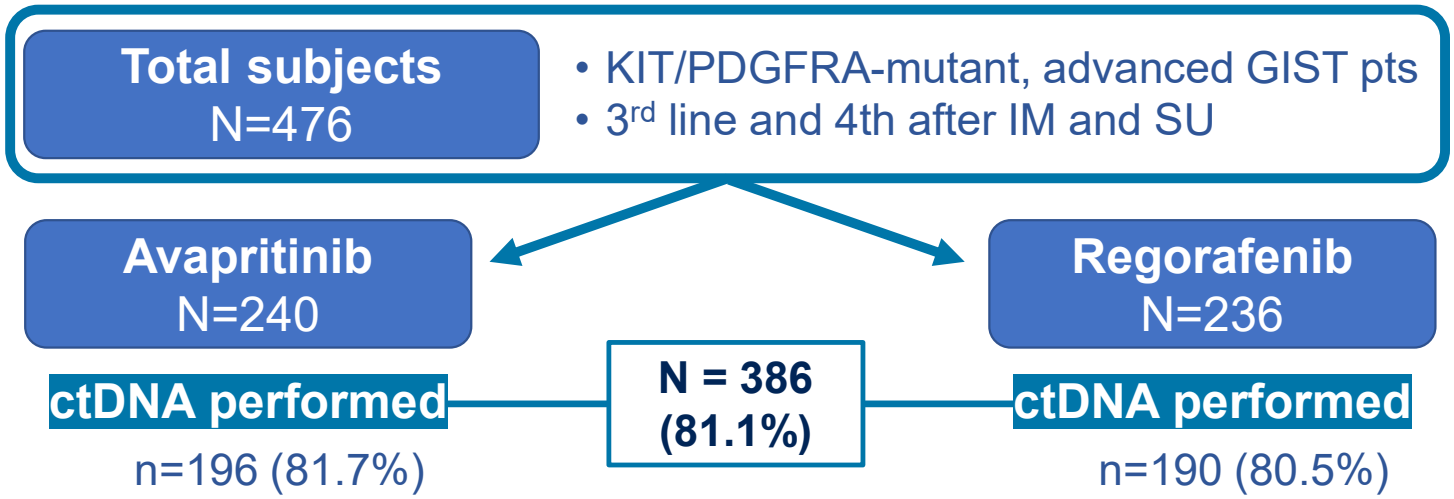
Results: detection of KIT/PDGFRA variants at baseline



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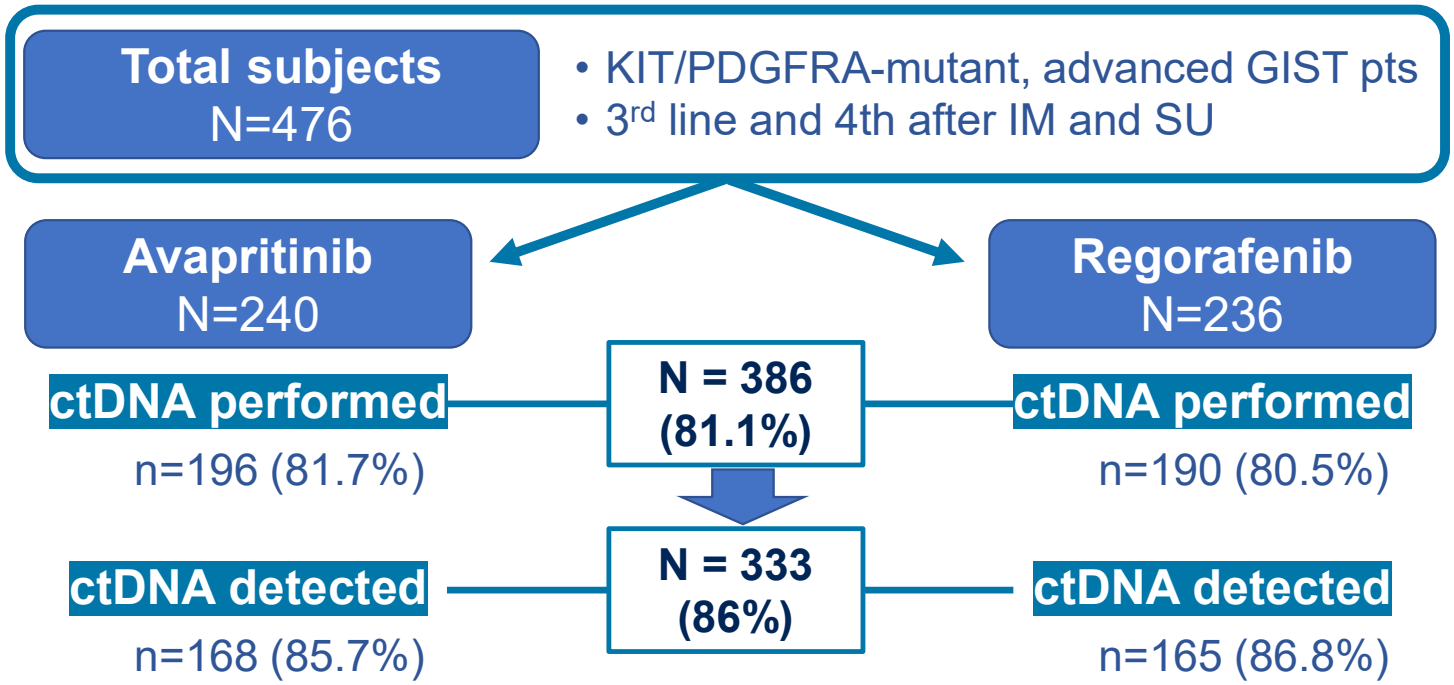

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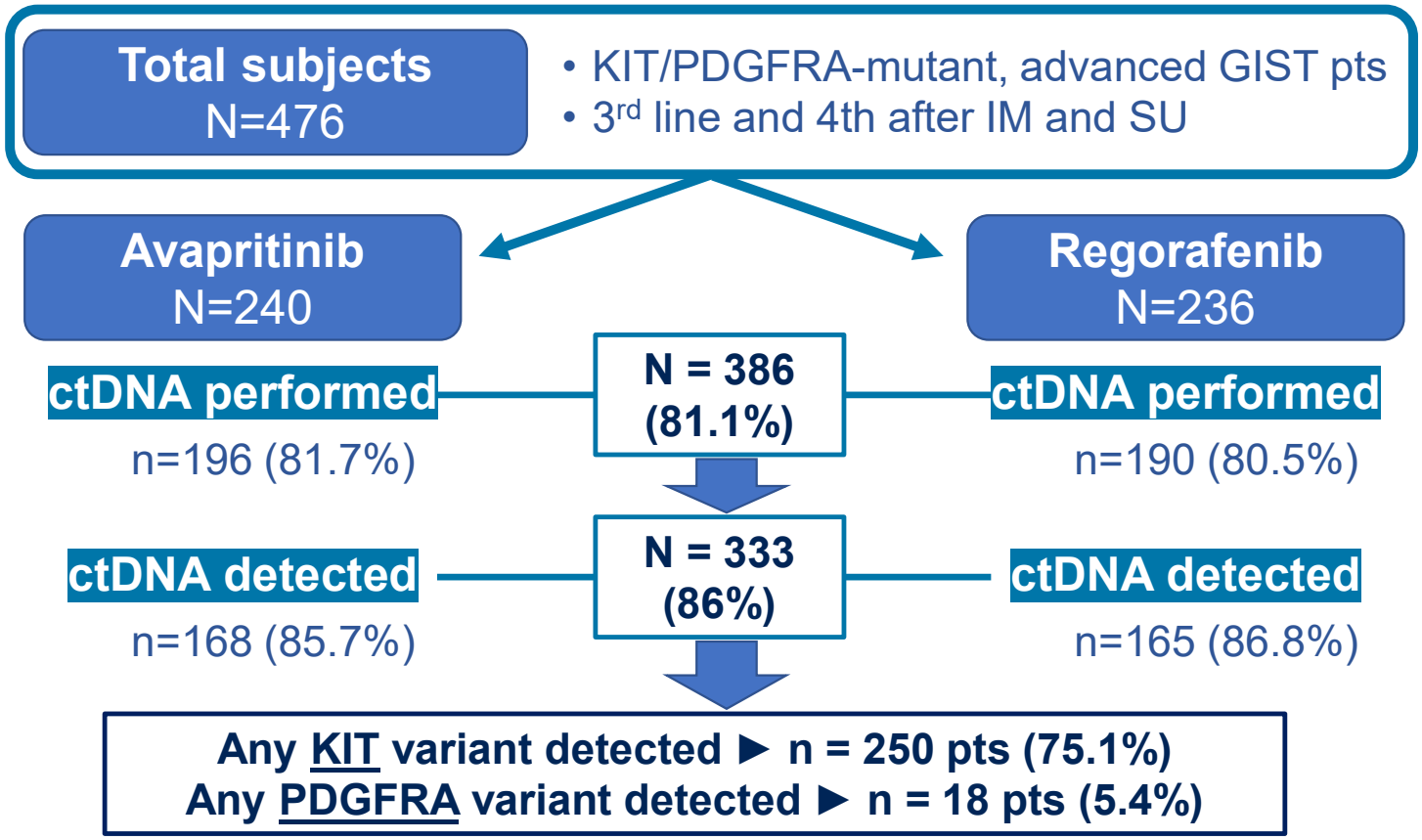

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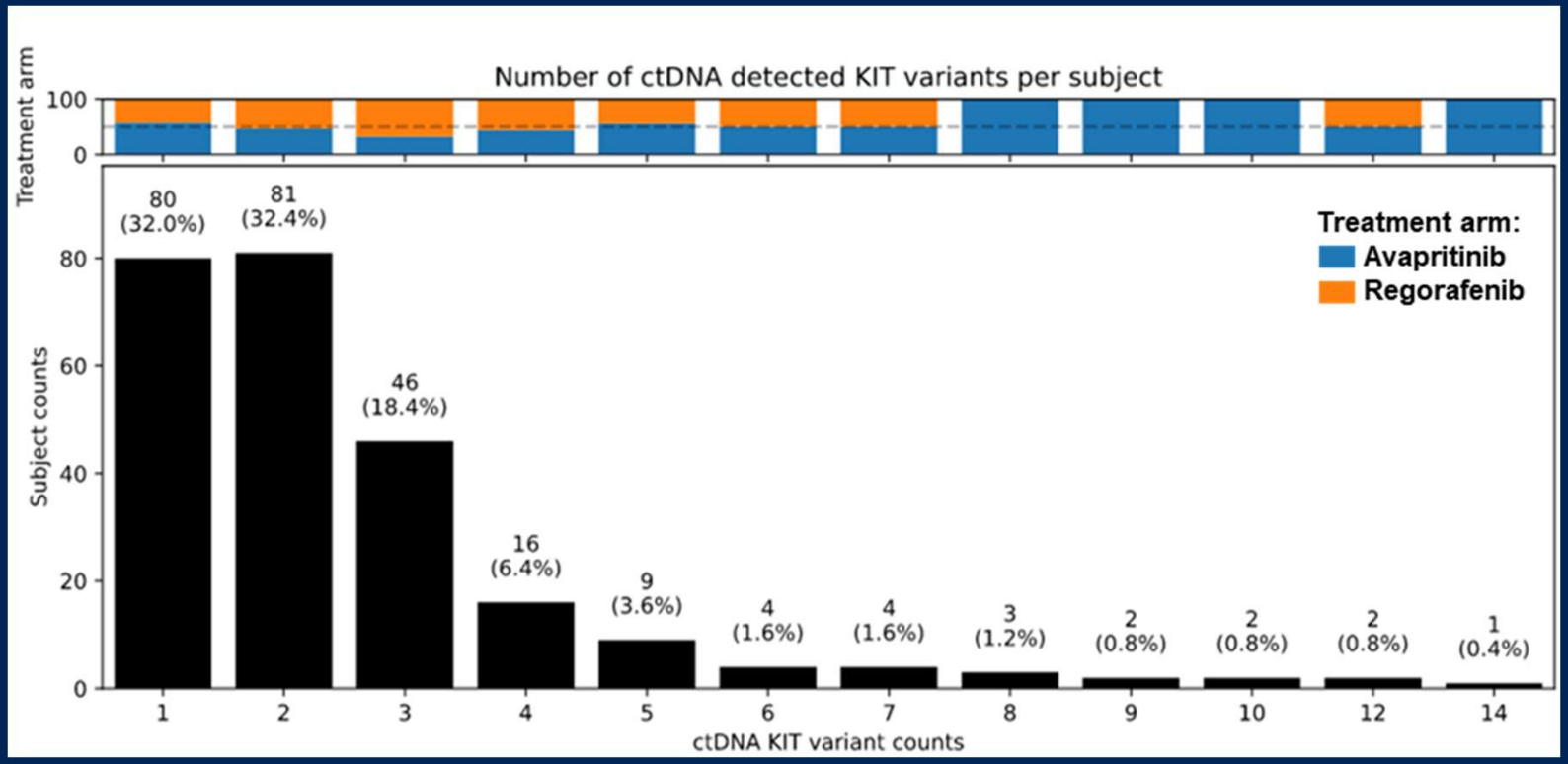
Landscape of KIT mutations: heterogeneity (1)

- **Number of ctDNA detected KIT variants per subject**



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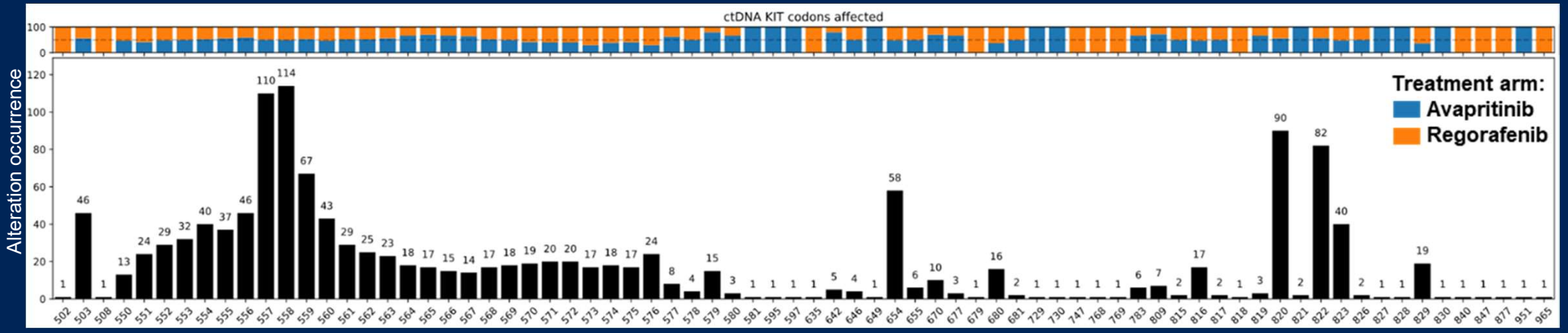
Landscape of KIT mutations: heterogeneity (2)

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



KIT primary mutations | **KIT secondary mutations**

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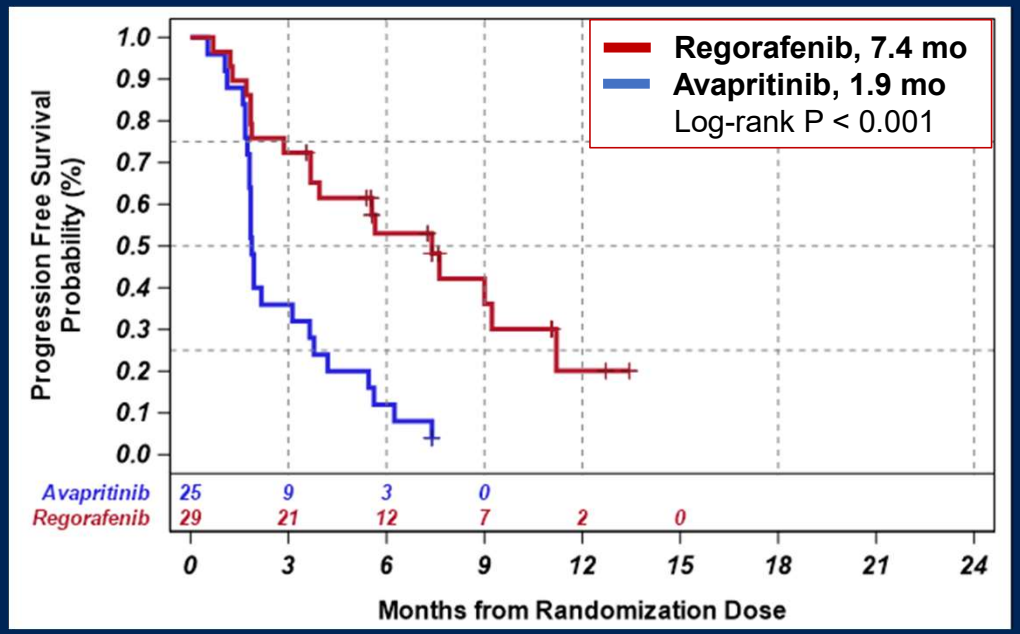
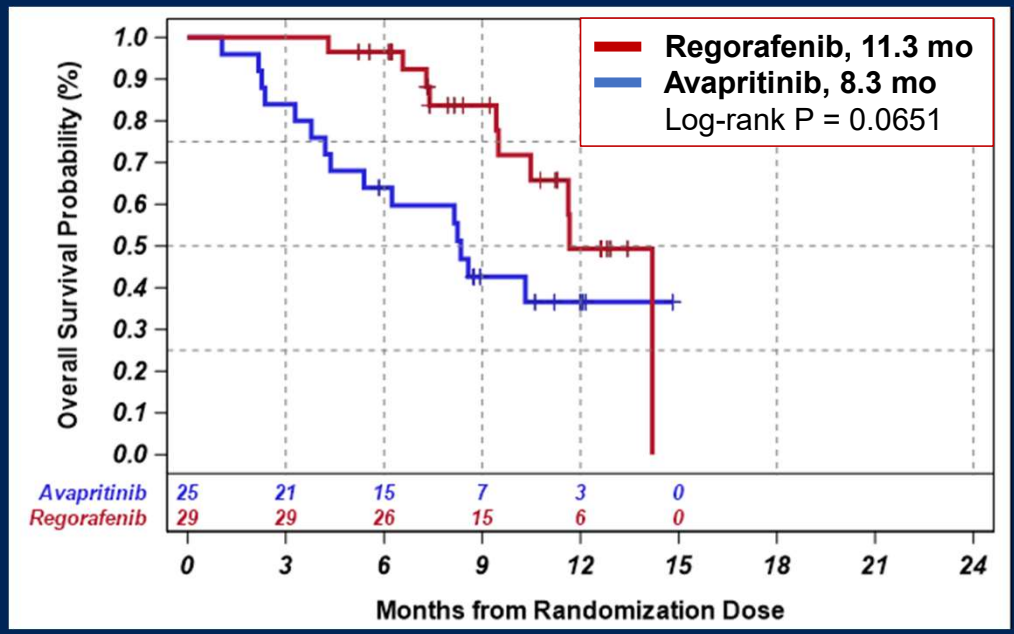
ctDNA mutations & outcomes: **ATP-binding pocket**

Shorter mPFS and mOS in patients with ctDNA+ ATP binding pocket mutations treated with AVAPRITINIB v. REGORAFENIB

Median PFS



Median OS



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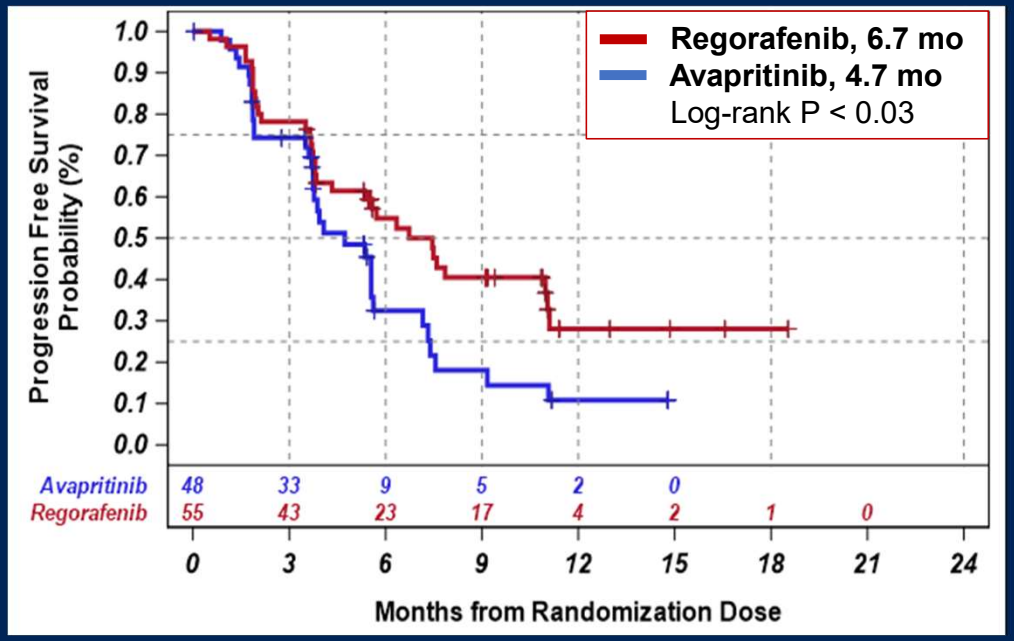
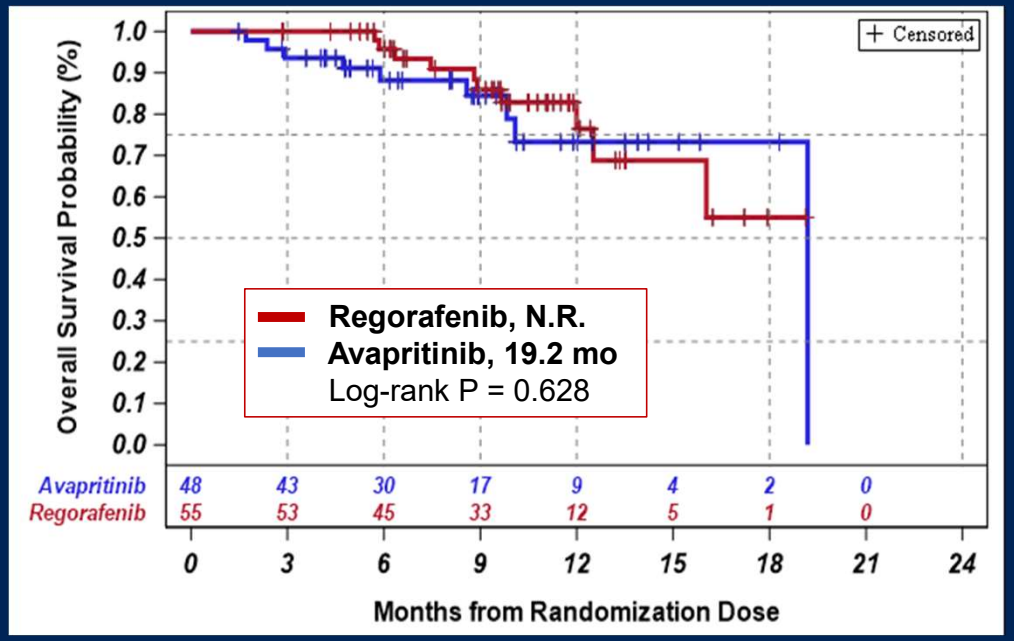
ctDNA mutations & outcomes: **Activation loop**

Shorter mPFS in patients with ctDNA+ Activation loop mutations (in the absence of ATP-BP mutants) treated with AVAPRITINIB v. REGORAFENIB

Median PFS



Median OS



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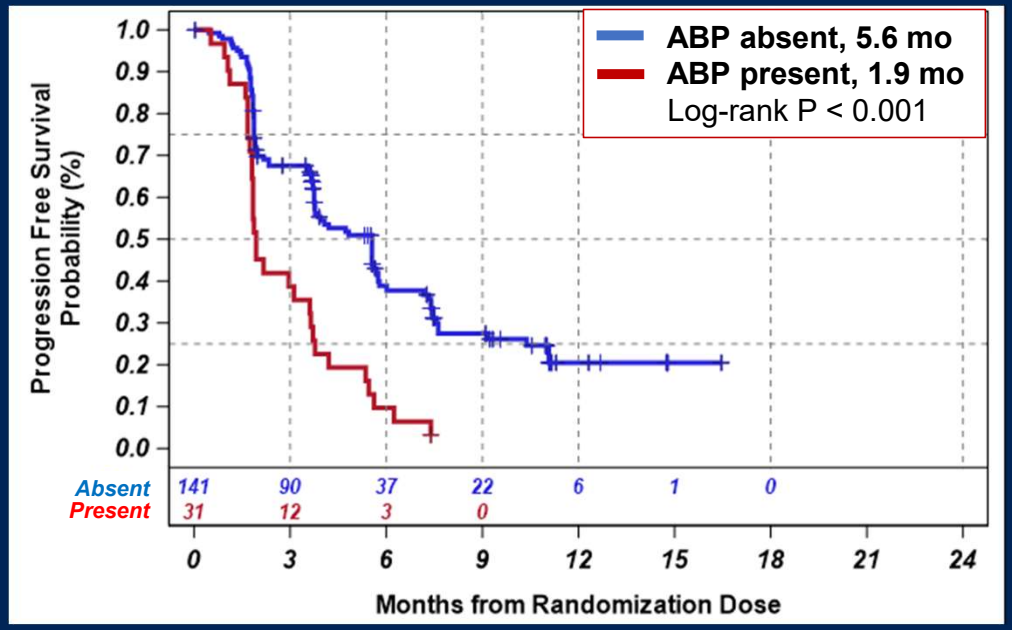
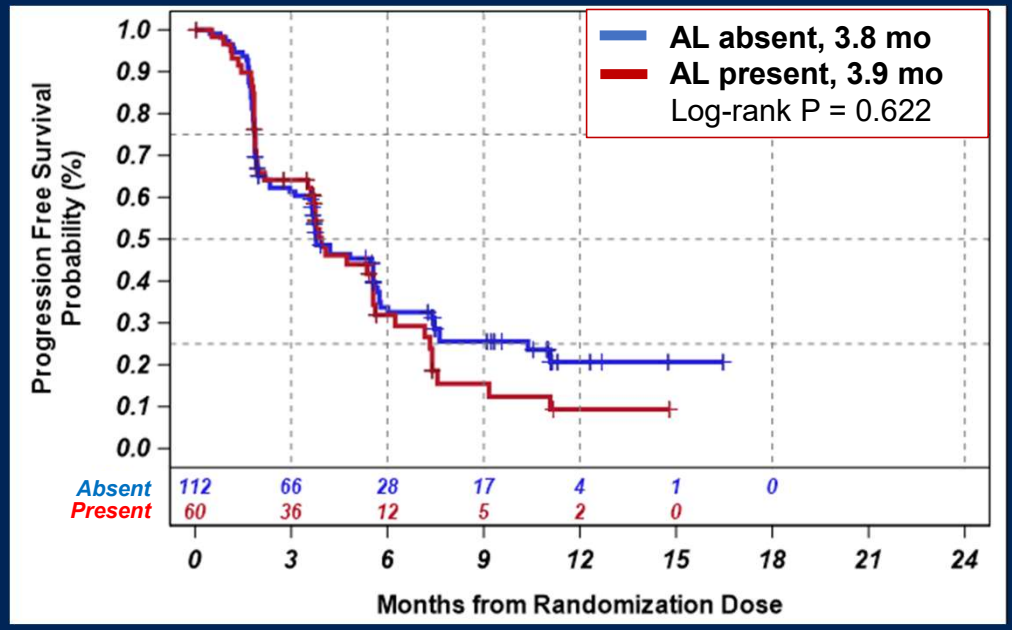
ctDNA mutations & outcomes: **Avapritinib**

mPFS on **AVAPRITINIB** is longer when **ctDNA secondary mutations in the ATP binding pocket** are absent

Median PFS – ATP binding pocket



Median PFS – Activation loop



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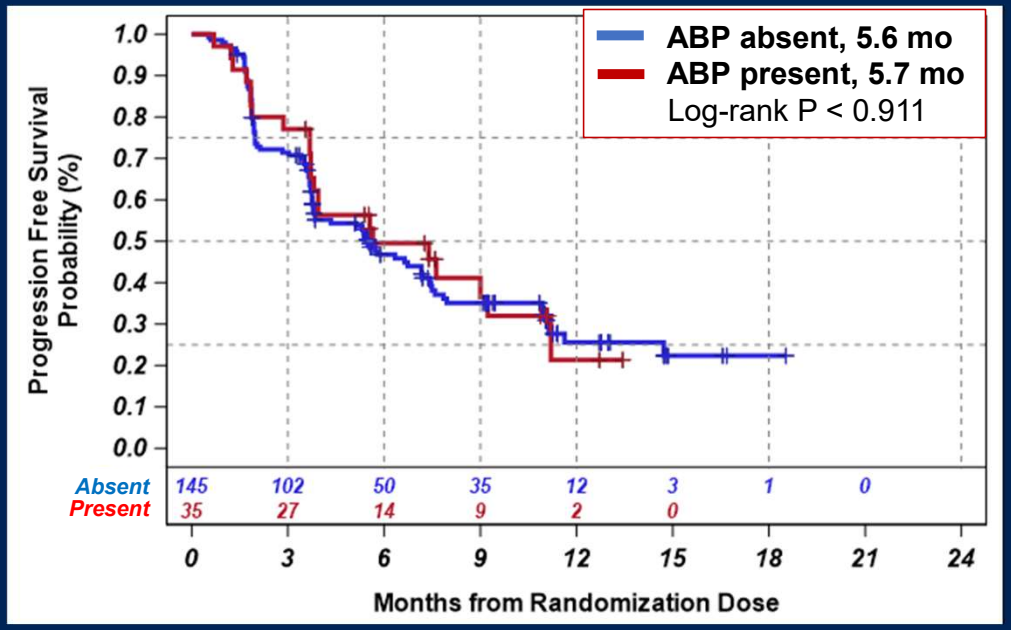
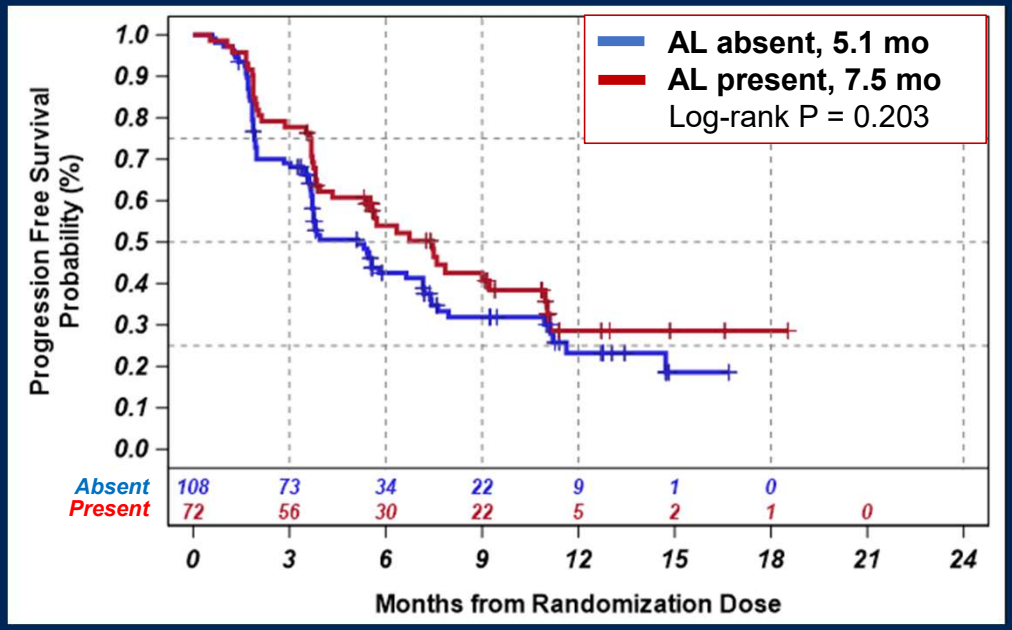
ctDNA mutations & outcomes: **Regorafenib**

REGORAFENIB showed similar activity regardless KIT mutational status and the location of KIT mutation

Median PFS – ATP binding pocket



Median PFS – Activation loop



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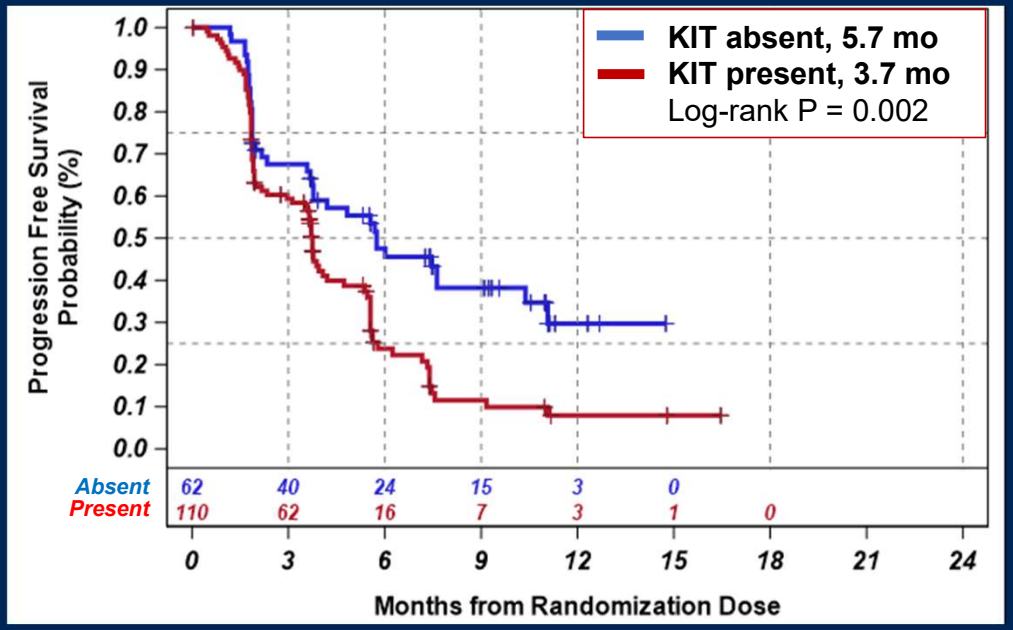
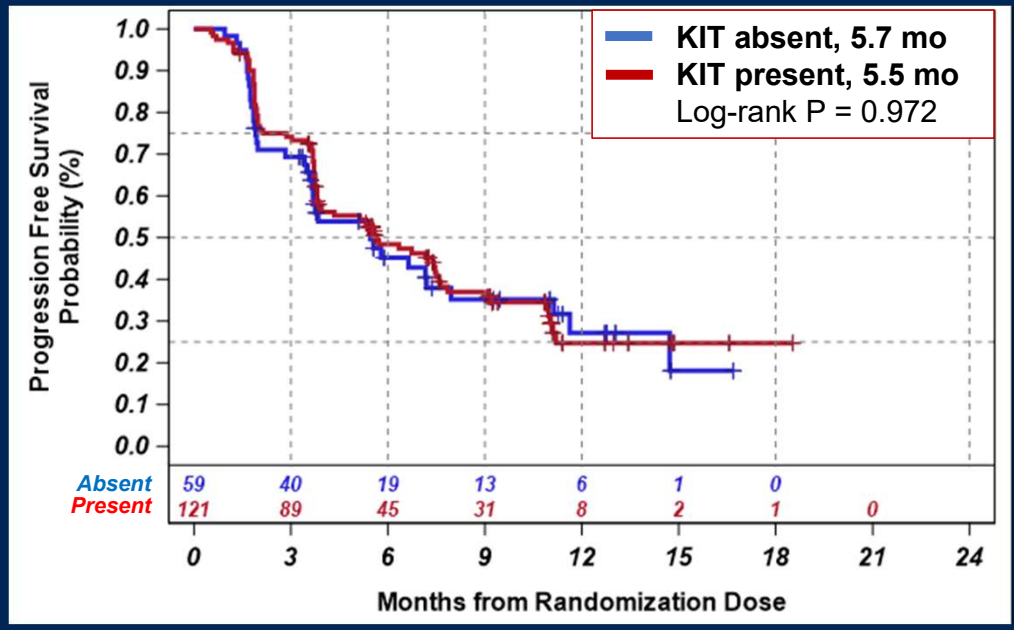
ctDNA mutations & outcomes: **ctDNA negative for KIT mut**

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

Median PFS – avapritinib



Median PFS – regorafenib



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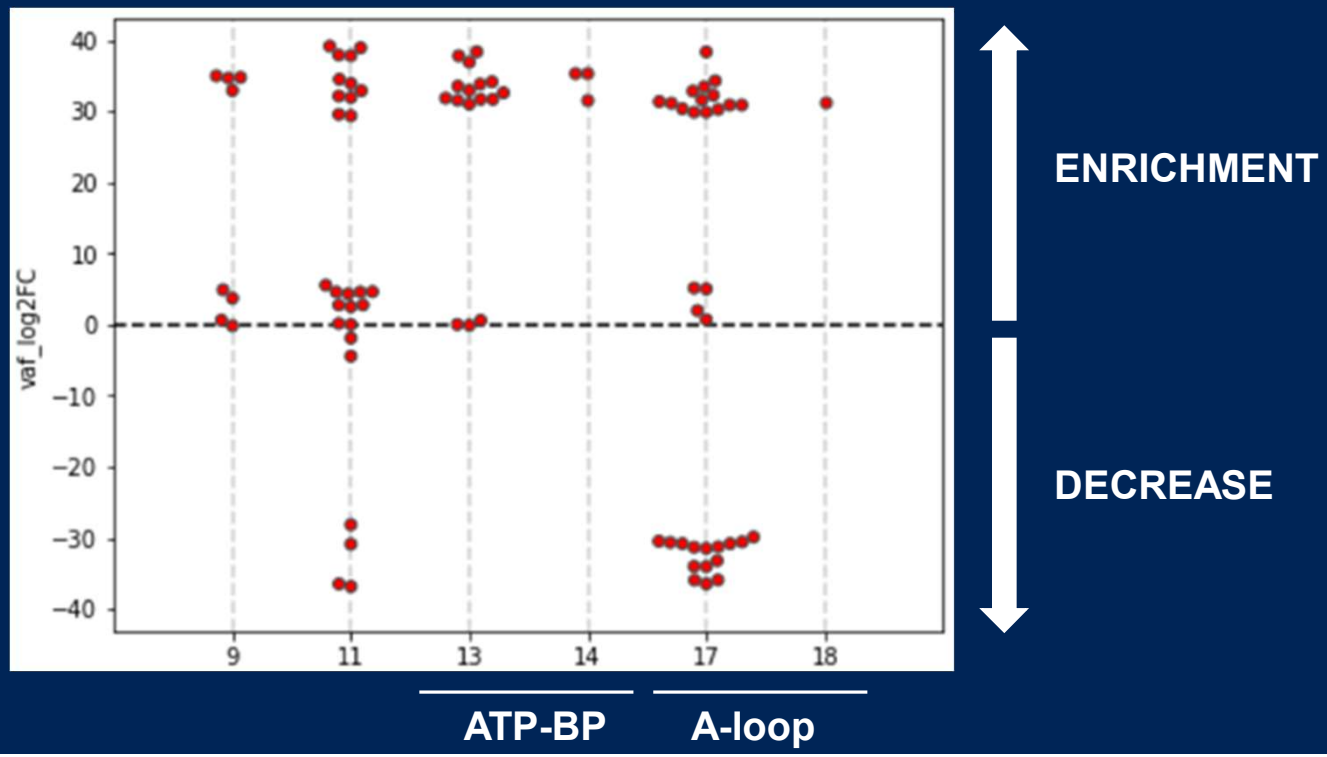
End of Treatment: **Resistance to avapritinib (n=42)**

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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Conclusions

- This is the first study to address the utility of ctDNA sequencing in advanced GIST in the context of a **large, international phase III clinical trial**.
- Hybrid capture-based plasma sequencing **detects KIT primary and secondary mutations** in the majority of TKI-resistant GIST patients.
- ctDNA studies reveals important **inter- and intra-patient heterogeneity** of KIT secondary mutations after progression to imatinib and sunitinib.
- **ctDNA sequencing correlates with outcomes in pretreated GIST**. Identification of ATP binding pocket mutations in KIT negatively correlates with avapritinib activity.
- The **multikinase inhibitory nature of regorafenib** may be relevant for its clinical activity regardless the type of KIT secondary mutation by plasma.

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