Characterization of the extensive heterogeneity of KIT/PDGFRA mutations in patients with fourth-line advanced gastrointestinal stromal tumor: Genomic analysis of the phase 3 INVICTUS study

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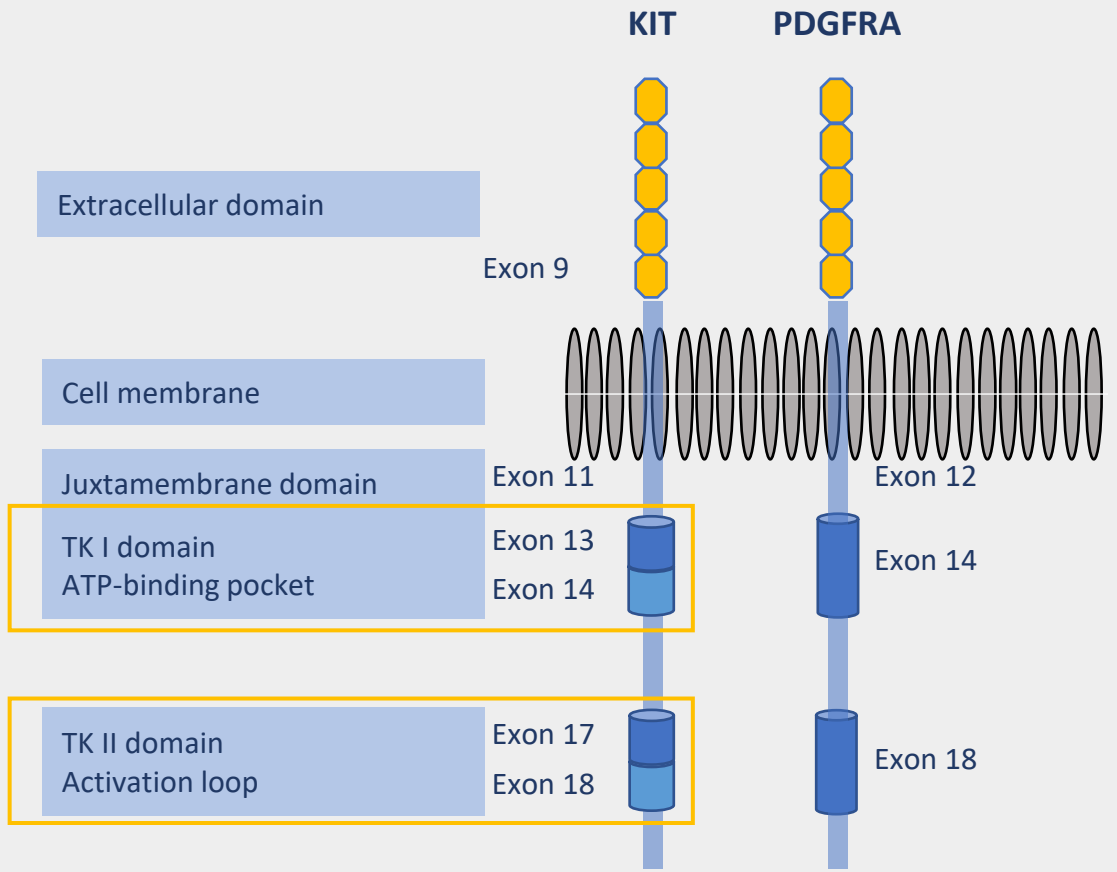
Disclosure information

Dr. Sebastian Bauer

- Received honoraria from Bayer, Eli Lilly, Novartis, Pfizer, and PharmaMar
- Serves in an advisory/consultancy role for ADC Therapeutics, Bayer, Blueprint Medicines, Daiichi Sankyo, Deciphera, Eli Lilly, Exelixis, Janssen-Cilag, Nanobiotix, Novartis, PharmaMar, Plexxikon, and Roche
- Receives research funding from Novartis
- Serves as a member of the External Advisory Board of the Federal Ministry of Health for “Off-label use in oncology”

Introduction

- KIT mutations in exon 11 and exon 9 are early oncogenic events in gastrointestinal stromal tumors (GIST), and clonal evolution of additional mutations within the kinase domains (exons 13, 14, 17, and 18; **Figure**) represent the major mechanism of resistance to KIT tyrosine kinase inhibitors (TKI)[1–4]
- In May 2020, the FDA approved ripretinib for the treatment of adult patients with advanced GIST who have received prior treatment with ≥3 kinase inhibitors, including imatinib
- Ripretinib is a switch-control TKI designed to inhibit mutant KIT and PDGFRA kinases[5]
- Baseline tumor and plasma samples were collected to investigate the genomic heterogeneity of resistance in the well-defined patient cohort (≥fourth-line) of the INVICTUS trial[5]



Adapted from Ding, et al. 2020 and Corless, et al. 2011
ATP, adenosine triphosphate; TK, tyrosine kinase.

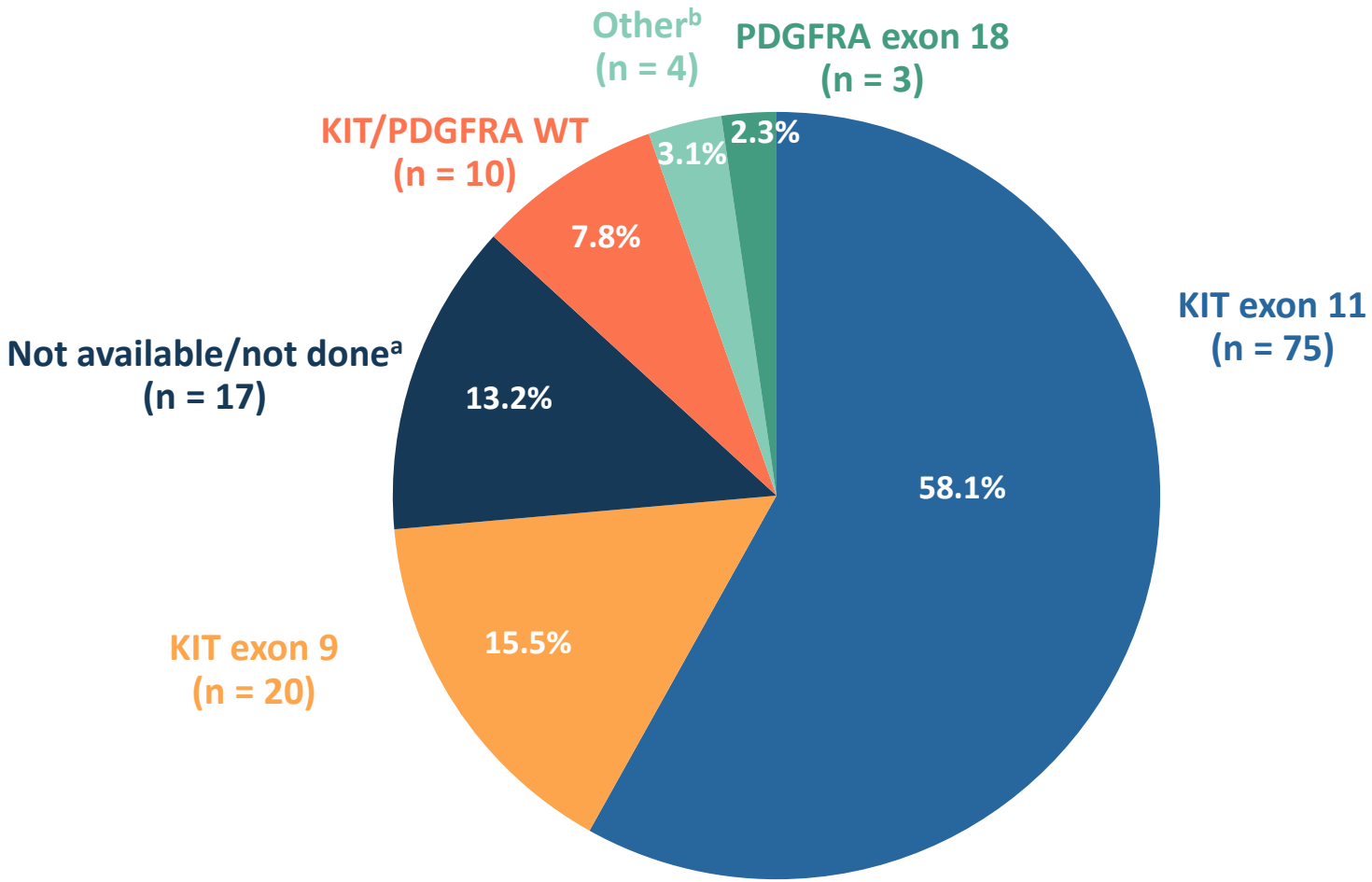
1) Nishida T, et al. *Gastric Cancer.* 2016;19:3–14. **2)** Serrano C, et al. *Ther Adv Med Onc*. 2014;6:115–27. **3)** NCCN Guidelines. Soft Tissue Sarcoma. Version 2.2020. **4)** Hemming ML, et al. *Ann Oncol*. 2018;29:2037–45. **5)** Blay J-Y, et al. *Lancet Oncol*. 2020;21:923–34.

Introduction/Methods

	Tissue biopsy	Liquid biopsy
Accessibility of testing material	• Archival tumor tissue is not always available and can be time consuming to retrieve • Invasive procedure is required to obtain biopsy • Biopsy with low tumor content cannot be used for genotyping	Noninvasive, minimal burden for patients
Data quality	High sensitivity and specificity	• High sensitivity, but false negative rate is high due to low shedding from the tumor • Can be challenging to use to identify emerging resistance mutations due to generally very low mutant allele frequency (<1%)

- Tumor tissue specimens were collected after the last anti-cancer therapy and were analyzed using a next-generation sequencing (NGS) 324-gene assay, FoundationOne
- Plasma samples were collected at baseline and analyzed via an NGS 73-gene liquid biopsy assay, Guardant360

Primary mutation subgroups by baseline tumor biopsy

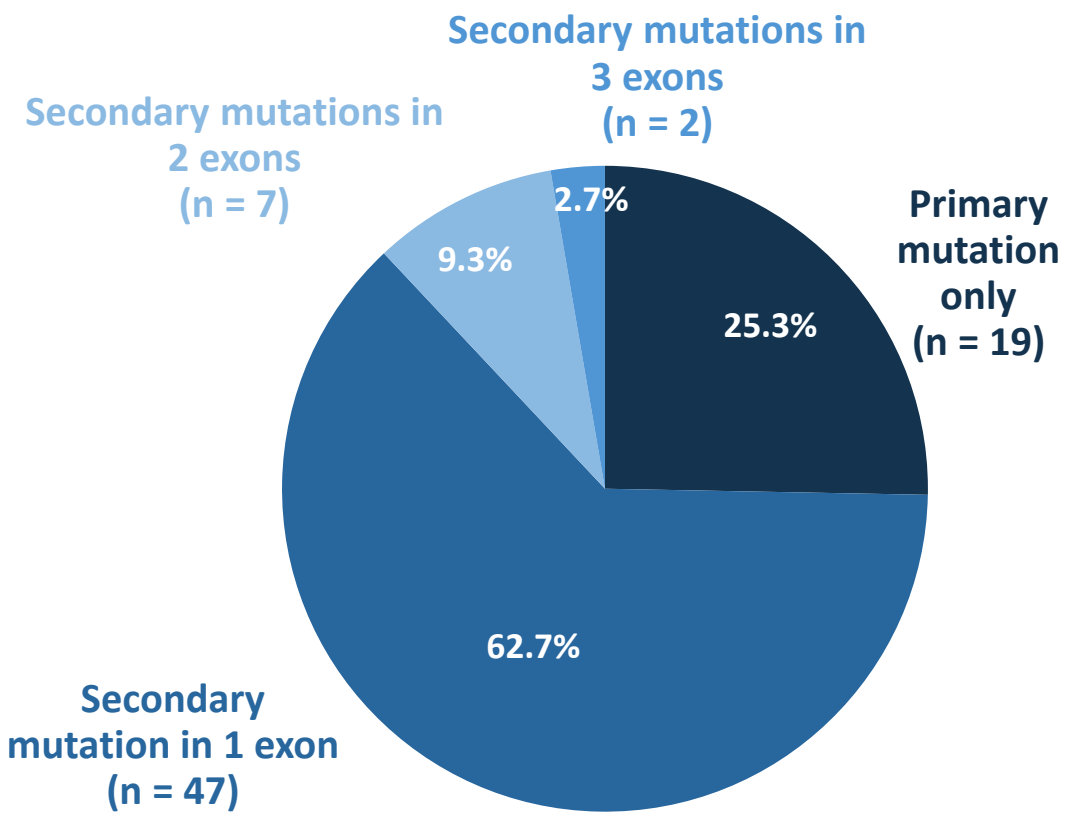


129 patients were enrolled in the INVICTUS study

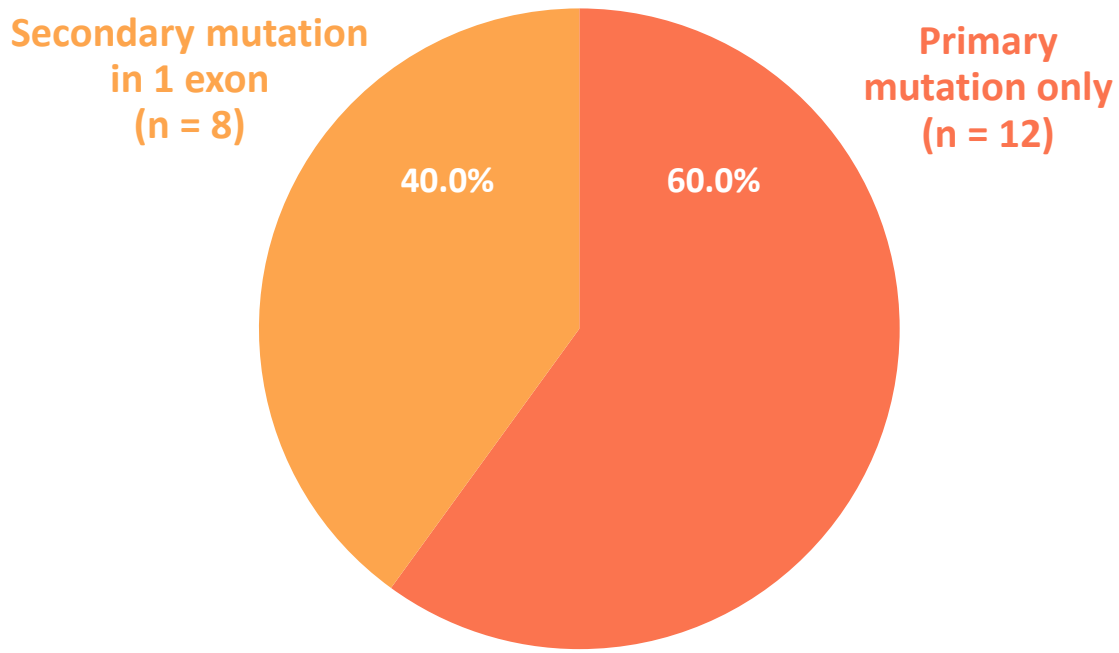
[a]Includes patients that failed sequencing due to low tumor content and a patient with no specimen.
[b]Includes 1 patient with a KIT exon 13 only mutation, 2 patients with KIT exon 17 only mutations, and 1 patient with KIT exon 13+17 mutations.
WT, wild type.

Secondary KIT mutations detected in tumor biopsy

Primary KIT exon 11 (N = 75)

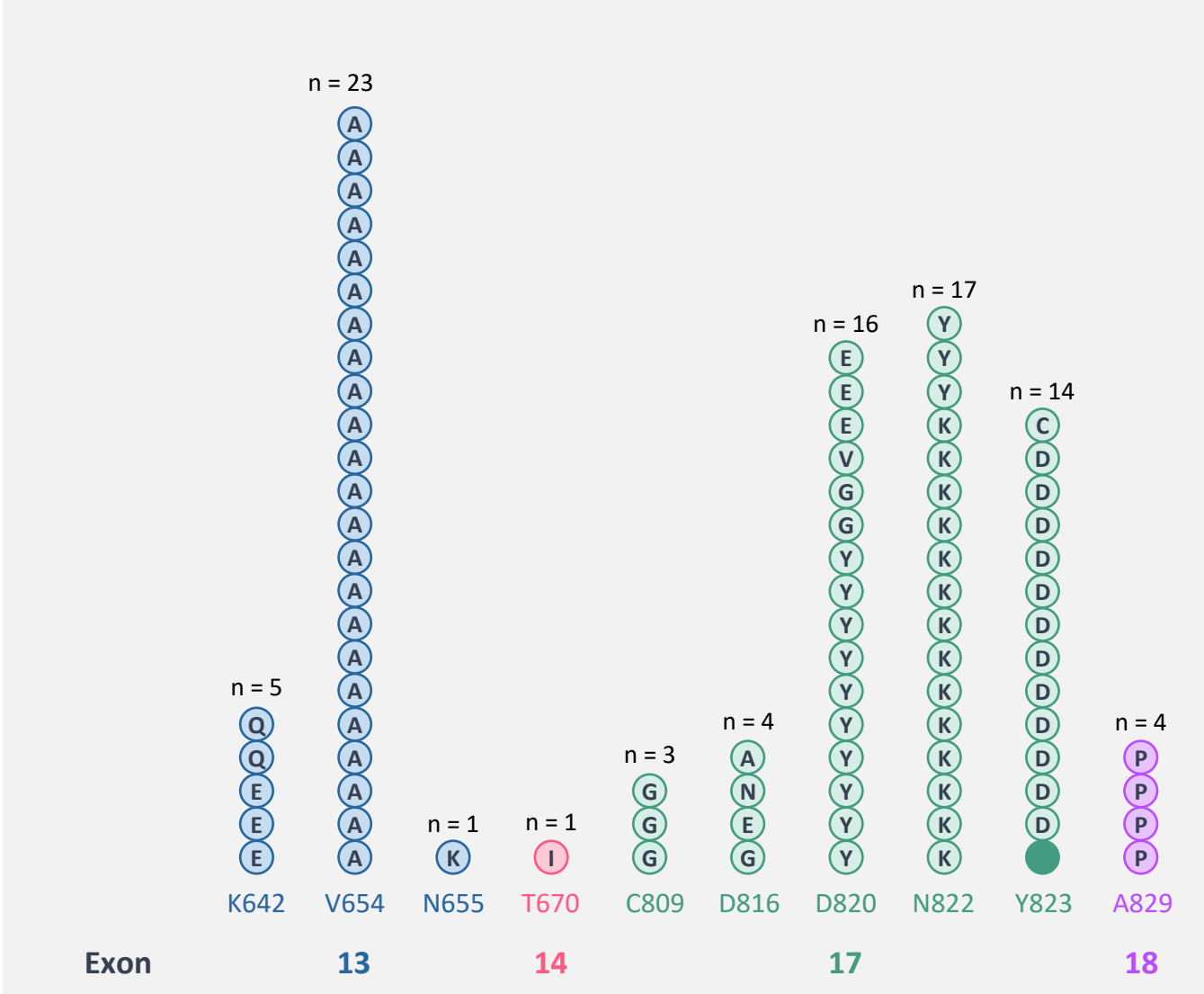


Primary KIT exon 9 (N = 20)



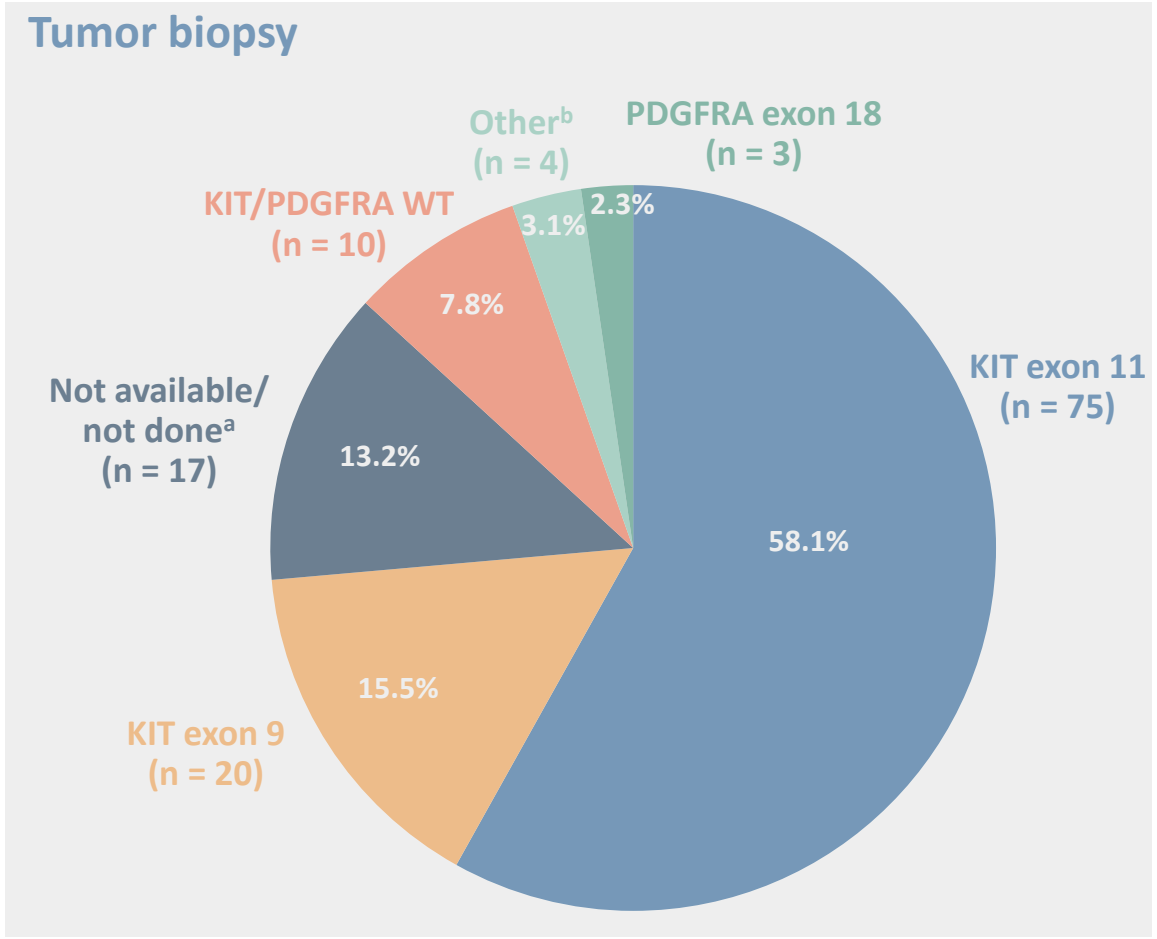
KIT mutations detected outside of exons 9/11 in tumor biopsy

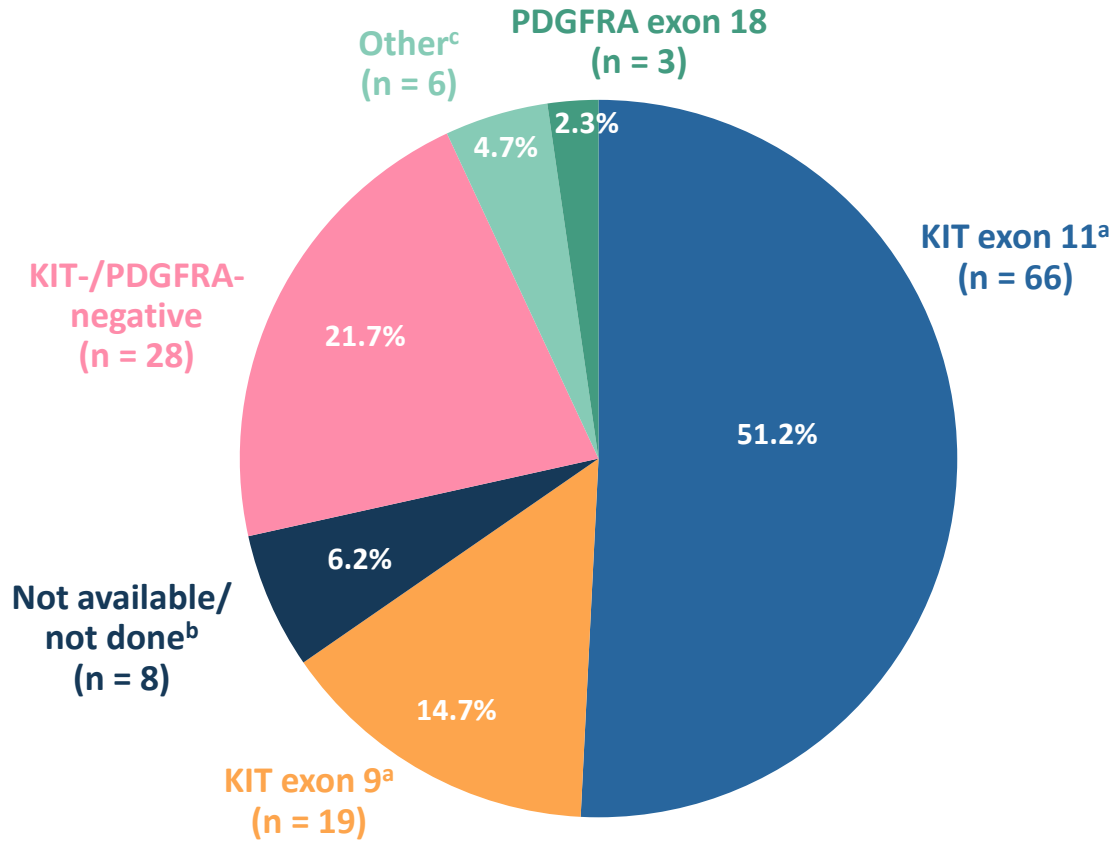
- Mutations were more diverse in exons 17/18 (activation loop) compared with exons 13/14 (ATP binding pocket)
- **Fifteen** different mutations were found in exons 17/18
- **Five** different mutations were found in exons 13/14



Open circle indicates the protein change that occurred; closed circle indicates an in-frame deletion.

Primary mutation subgroups by baseline liquid biopsy



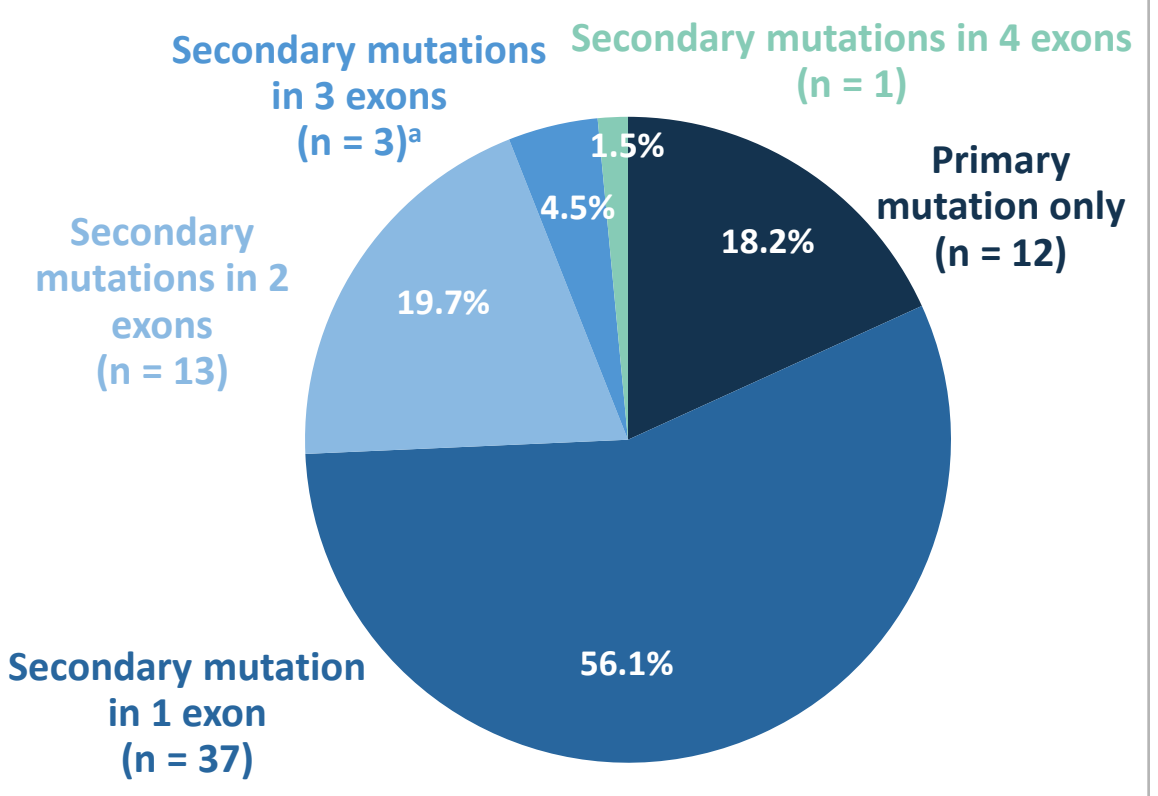


129 patients were enrolled in the INVICTUS study

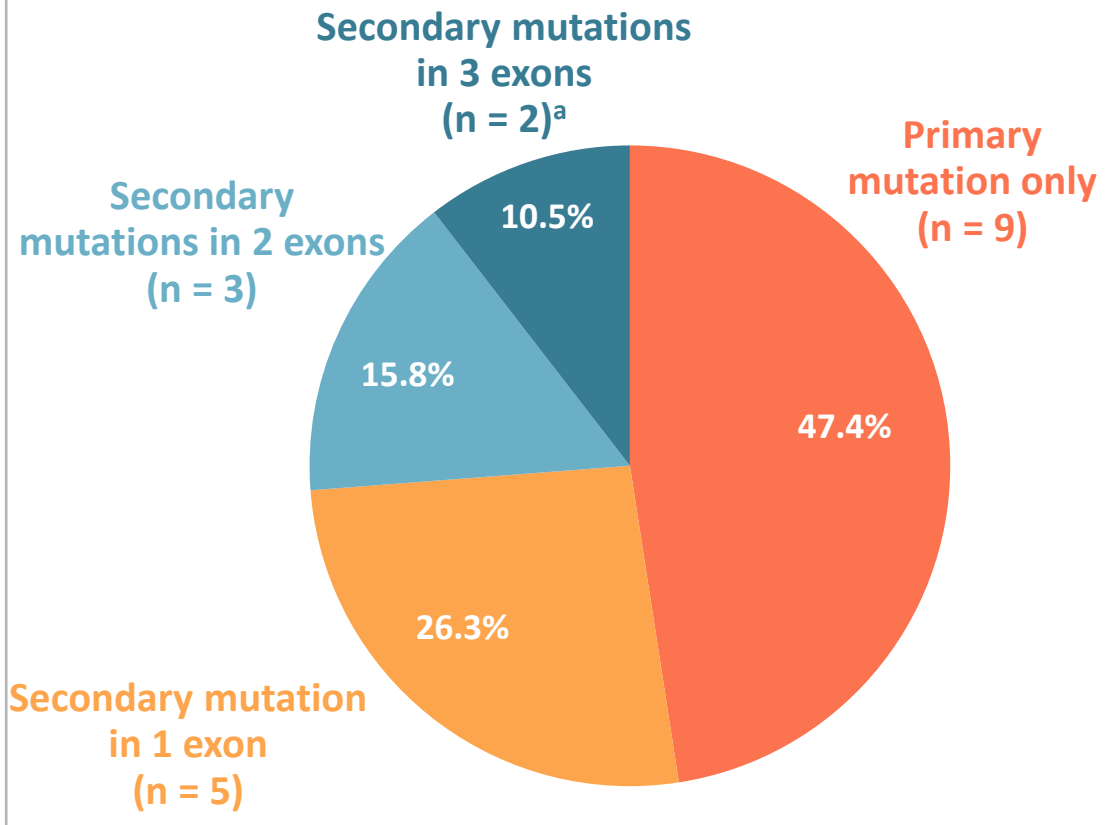
[a] KIT exon 9 and 11 mutations were both detected in 1 patient and were counted in both groups.
[b] Includes patients that failed sequencing due to low tumor content and patients with no specimen.
[c] Includes 3 patients with exon 13 only mutations, 1 patient with an exon 17 only mutation, 1 patient with exon 13+17 mutations, and 1 patient with exon 13+14+17 mutations.

Secondary KIT mutations detected in liquid biopsy

Primary KIT exon 11 (N = 66)



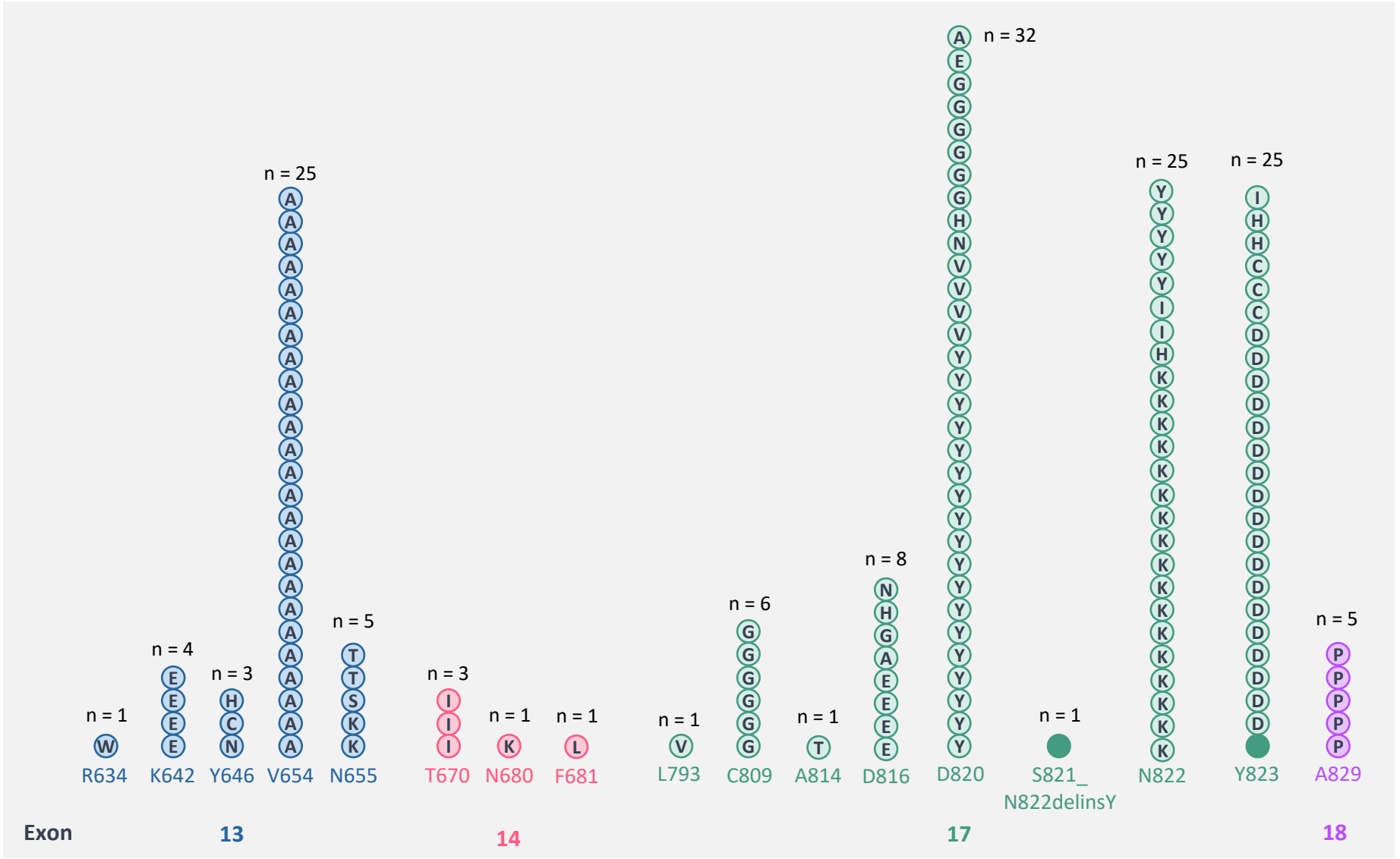
Primary KIT exon 9 (N = 19)



[a]One patient had both KIT exon 9 and 11 mutations.

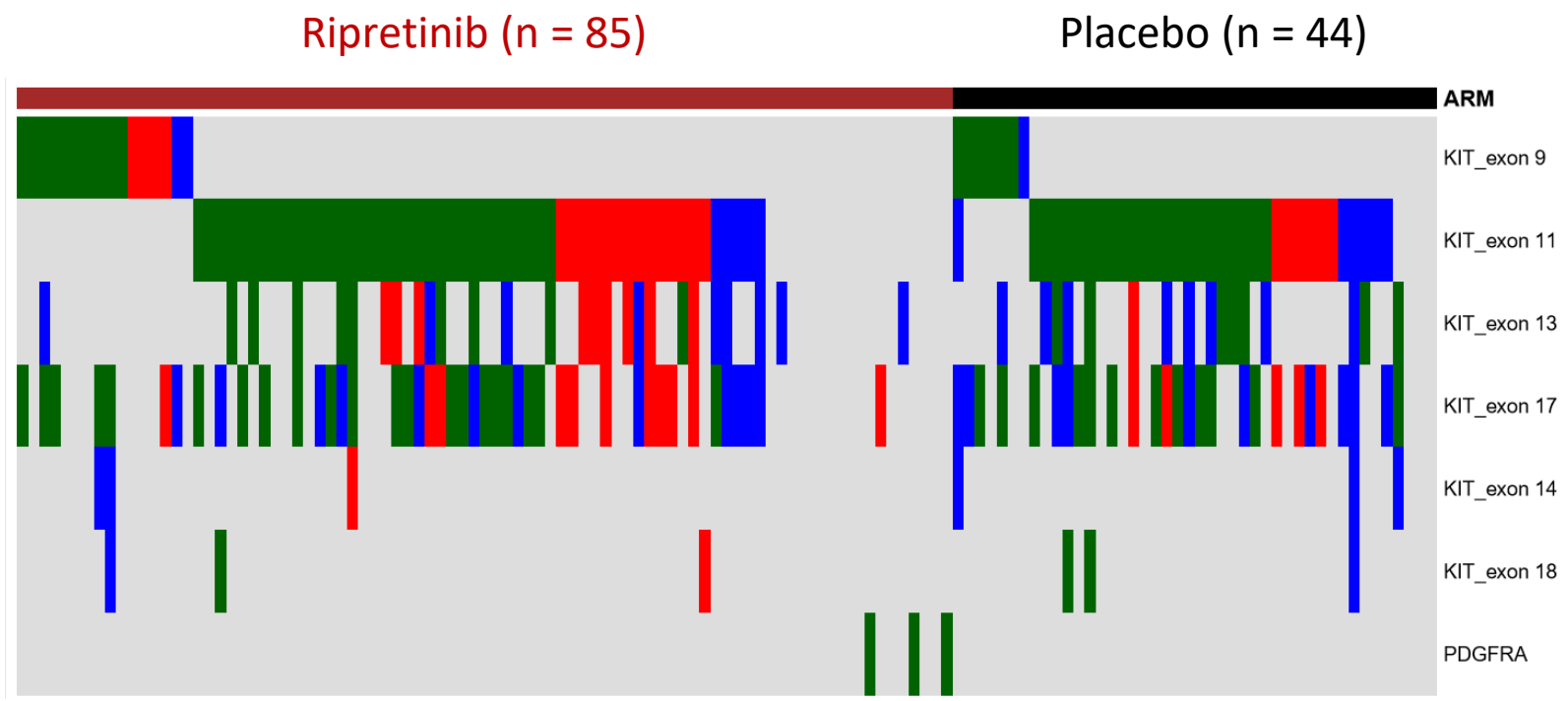
KIT mutations detected outside of exons 9/11 in liquid biopsy

- More mutations were detected via liquid biopsy compared with tumor biopsy
- **Twenty-six** different mutations were found in exons 17/18
- **Twelve** different mutations were found in exons 13/14



Open circle indicates the protein change that occurred; closed circle indicates an in-frame deletion.
There were 3 patients with exon 13 only mutations, 1 patient with an exon 17 only mutation, 1 patient an exon 13+17 mutation, and 1 patient with an exon 13+14+17 mutation.

Spectrum of KIT/PDGFRA mutations detected in tumor and liquid biopsy



Green: detected in both; red: detected in tumor only; blue: detected in liquid only

- Heat map is generated by KIT exons/PDGFRA rather than by specific mutations in each exon
- Three patients were identified as having PDGFRA non-D824V exon 18 mutations

Conclusions

- This is the first and largest baseline genomic analysis by tumor and liquid biopsy in fourth-line patients with GIST that failed prior treatment with at least imatinib, sunitinib, and regorafenib
- The combination of tumor and liquid biopsies increased the detection rate of secondary mutations
- In patients with ≥fourth-line GIST from the INVICTUS study, we observed a complex and heterogeneous mutational landscape
- The heterogeneity of these mutations highlight the need for therapies that are effective against a broad spectrum of mutations

Acknowledgments

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