Multi-omic characterization of gastrointestinal stromal tumor (GIST) in a large real-world patient cohort

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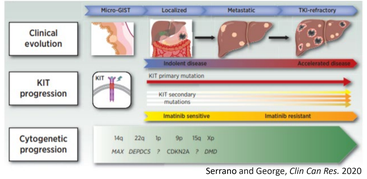
Background

- Molecular knowledge of GIST is limited due to its rarity, few genes have been identified as relevant determinants of outcomes, tumor evolution and therapeutic targets. Therefore, we aimed to dissect the GIST molecular landscape in the largest series of real-world patients reported to date.



Serrano and George, *Clin Can Res.* 2020

Methods

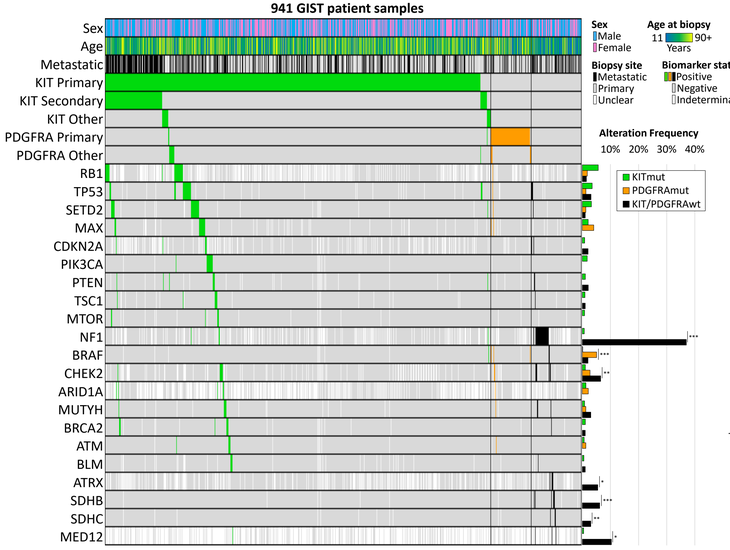
- 941 GIST patient samples
- Next-gen sequencing
  - DNA (592-gene, N = 493; whole exome, N = 448)
  - RNA (whole transcriptome, N = 592)
- Gene expression signatures
  - Proliferation (Cristescu, 2021)
  - Cell cycle activation (CINSARC; Chibon, 2010)
  - Inflammation (T-cell inflamed; Ayers, 2017)
- Tumor microenvironment
  - Cell population abundance was estimated using MCP-counter (Becht, 2016)
- Statistical significance tested by χ^2, Fisher's exact, or Mann-Whitney U as appropriate.

Cohort demographics	
Samples, N	941
Age	
Median years (range)	64 (11 - 90+)
Sex	
Male	488 (51.9%)
Female	453 (48.1%)
Biopsy site	
Primary	533 (59.2%)
Metastatic	368 (40.8%)
Unclear	[40]

Results

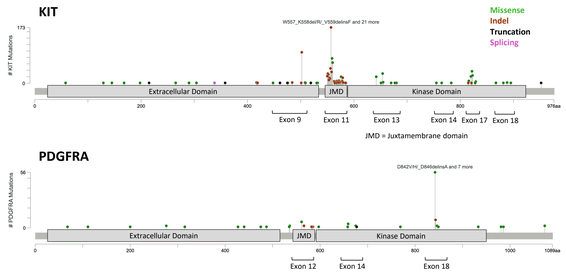
GIST molecular landscape

- Study cohort was comprised of 81% (N = 762) ***KIT*mut**, 8.5% (N = 80) ***PDGFRA*mut**, and 10.5% (N = 99) ***KIT/PDGFRA* wild-type (wt)**, with 14.8% (N = 140) samples harboring a secondary KIT variant suggestive of TKI resistance
  - **KIT Primary** = mutation in exon 9, 11, or 13 (K642E/Q)
  - **KIT Secondary** = mutation in exon 13 (651-655), 14, 17, or 18
  - **PDGFRA primary** = mutation in exon 12, 14, or 18
- DNA alterations (SNVs/indels):
  - Overall median TMB was 2 mutations/MB (range 0-13)
  - ***KIT/PDGFRA*wt** were identified with mutations in *NF1* (33.7%), DNA repair genes (16.7%), *SDHX* (8.2%), *BRAF* (6.3%), and *PTEN* (1.9%), along with NTRK3 fusions (3.1%)
  - ***KIT/PDGFRA*mut** infrequently harbored *RB1*, *TP53*, *SETD2*, *ARID1A*, *PIK3CA*, *PTEN*, *TSC1*, *BRCA1*, or *CHEK2* co-mutations (1-5% each).
- Copy number amplification (≥6 copies)
  - Overall uncommon (≤2% for all genes)



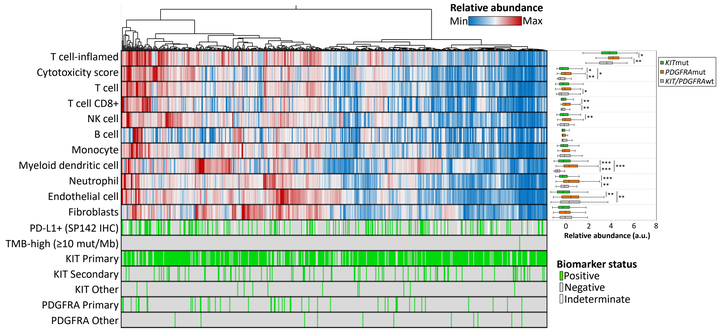
KIT and PDGFRA variants occur in key functional domains

- **Primary *KIT*** variants: occurred in exons 11 (83.5%), 9 (13.9%), and 13 (2.6%).
- **Secondary *KIT*** variants: comprised 14.6% of total *KIT* mutations.
  - Distributed across the ATP binding pocket (36.8%) and activation loop (63.2%).
- **Primary *PDGFRA*** variants: occurred in exons 18 (80.0%), 12 (14.2%), and 14 (5.9%).



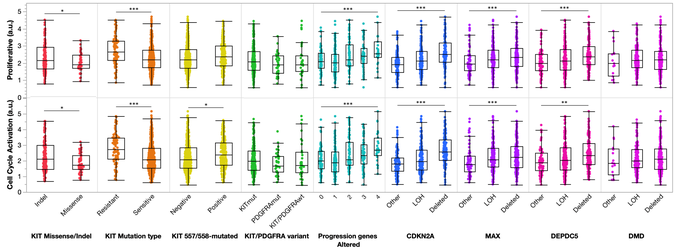
GIST tumor microenvironment

- Compared to ***KIT*mut** and ***KIT/PDGFRA*wt**, ***PDGFRA*mut** had increased abundance of several immune cell populations (range 1.2-3.7-fold, $p < 0.05$), along with enhanced inflammation signatures (1.1- and 1-2-fold, $p < 0.05$).



Variants associated with increased signatures of proliferation

- Proliferation and cell cycle activation signatures:
  - Increased in ***KIT*** exon 11 indels v. missense mut
  - Increased in ***KIT*** resistant v. ***KIT*** primary
  - No difference between ***KIT*** exon 11 557/558 v. others
  - No difference between ***KIT*** v. ***PDGFRA*** v. ***KIT/PDGFRA*wt** subgroups
- Deletion of tumor progression genes:
  - ***MAX*** (40.0%), ***CDKN2A*** (32.3%), and ***DEPDC5*** (33.9%) associated with increased proliferative gene expression
- Proliferation signature not increased with ***DMD*** deletion (52.5%)



Conclusions

- This series provides unprecedented resolution of *KIT/PDGFRA*mut GIST with features of clinical aggressiveness associated with *KIT* exon 11 indels and resistance mutations, illustrating a specific cytogenetic genotype with more aggressive growth and malignant behavior.
- Identification of less common molecular alterations that drive kinase activation and impaired DNA damage repair warrant further investigation.

References

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ASCO Annual 2023