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\(^5\)

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Introduction/Methods

### Tissue biopsy

- 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

### Liquid biopsy

- Noninvasive, minimal burden for patients

### 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

### 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%)
Primary mutation subgroups by baseline tumor biopsy

- KIT exon 11 (n = 75)
- KIT/PDGFRA WT (n = 10)
- Not available/not done (n = 17)
- KIT exon 9 (n = 20)
- PDGFRA exon 18 (n = 3)
- Other (n = 4)

129 patients were enrolled in the INVICTUS study

- Includes patients that failed sequencing due to low tumor content and a patient with no specimen.
- 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)
- Secondary mutation in 1 exon (n = 47) 62.7%
- Secondary mutations in 2 exons (n = 7) 9.3%
- Secondary mutations in 3 exons (n = 2) 2.7%
- Primary mutation only (n = 19) 25.3%

### Primary KIT exon 9 (N = 20)
- Secondary mutation in 1 exon (n = 8) 40.0%
- Primary mutation only (n = 12) 60.0%
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

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*KIT exon 9 and 11 mutations were both detected in 1 patient and were counted in both groups.

*Includes patients that failed sequencing due to low tumor content and patients with no specimen.

*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.

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Secondary KIT mutations detected in liquid biopsy

**Primary KIT exon 11 (N = 66)**
- Secondary mutations in 3 exons (n = 3)
- Secondary mutations in 2 exons (n = 13)
- Secondary mutation in 1 exon (n = 37)
- Primary mutation only (n = 12)

**Primary KIT exon 9 (N = 19)**
- Secondary mutations in 3 exons (n = 1)
- Secondary mutations in 2 exons (n = 3)
- Secondary mutations in 3 exons (n = 3)
- Primary mutation only (n = 9)

*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

- 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

**Ripretinib (n = 85)**

**Placebo (n = 44)**

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