ctDNA-based genomic landscape analysis to evaluate molecular brake and gatekeeper mutations in FGFR2

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INTRODUCTION

FGFR2 and FGFR3 (FGFR2/3) in Cancer:

Receptor tyrosine kinases (RTKs) become aberrantly activated by gene rearrangements (including fusion), small indels, and point mutations. Validated therapeutic targets with approved small molecule inhibitors in cholangiocarcinoma & bladder cancer

FGFR2/3 fusion tumors can develop de novo, KRK competitive inhibition (pr1-gene) through secondary FGFR mutations that occur in the kinase domain, typically in the molecular brake and gatekeeper amino acids

Molecular Brake and Gatekeeper Mutations:

- The molecular brake is an autophosphorylation feature that consists of three amino acid residues, referred to as the regulatory triad in the FGFR kinase domain. Alterations in the molecular brake amino acids reduce autoinhibition (i.e. kinase activation) and increase the binding of most 1st-gen proteins. Consistent with their activating function, molecular brake mutations are known to occur in both the resistance setting and in tumors that are FGFR-naïve
- Gatekeeper mutations cause steric clashes that can prevent binding of many FGFR inhibitors and they are typically identified in the setting of acquired resistance

METHODS

Analyses utilized Guardant360® (a unIntegrated clinical genomic research database spanning from March 2016 to Sept 2021) including 1,700,000+ patients with actionable/clinically relevant mutations identified with the liquid biopsy Guardant360® assay

- Analyses include FGFR2 or FGFR3 alterations that are at least likely to be oncogenic or confer resistance
- Counts of patients & alterations were grouped by their sensitivity to 1 targeted inhibitor
- FGFR2/3 oncogenic alterations are found in various cancer types and are likely to be primary drivers; the highest

RESULTS

Objective: To evaluate the occurrence and proportion of kinase domain resistance mutations in FGFR2/3 based on a real-world clinical genomic database of ctDNA.

FGFR2/3 alterations in various cancer types

Pan-Cancer Oncogenic FGFR2 & FGFR3 Alterations

- 1,700 Patients with oncogenic FGFR2/3 alterations (Figure 1)
- Four tumor types with a potential FGFR2/3 positive patient: NSCLC, Breast, Bladder, Cholangiocarcinoma (CCA)

FGFR2/3 oncogenic alterations are found in various cancer types and are likely to be primary drivers; the highest

FGFR2 gatekeeper and gatekeeper mutations are currently available FGFR2 inhibitors

- Patients with FGFR2/3 molecular brake and gatekeeper mutations may benefit from next-generation FGFR2/3 targeted therapies designed to inhibit a broad spectrum of both primary and secondary resistance mutations

CONCLUSIONS

- FGFR2/3 oncogenic alterations are found in various cancer types and are likely to be primary drivers; the highest

REFERENCES:

