PHASE I RESULTS FROM A MULTI-PHASE COMPREHENSIVE GENOMIC SEQUENCING TUMOR STUDY IN GASTROINTESTINAL STROMAL TUMOR PATIENTS

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INTRODUCTION

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. Most GISTs harbor a mutation located in either KIT or platelet-derived growth factor receptor alpha (PDGFRα). Over the last few decades, advances in GIST have led to the approval of multiple targeted therapies. Imatinib, one of the frequently used therapies for GIST, has demonstrated low sensitivity among KIT/PDGFRα wildtype GISTs. Comprehensive genomic profiling (CGP) is used to optimize the therapy selection due to its ability to detect undetected pathogenic biomarkers and allowing a more tailored approach to therapy in both primary and metastatic settings.

ABSTRACT

Objective

Gastrointestinal Stromal Tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. Most GISTs harbor a mutation located in either KIT or platelet-derived growth factor receptor alpha (PDGFRα). Over the last few decades, advances in GIST have led to the approval of multiple targeted therapies. Imatinib, one of the frequently used therapies for GIST, has demonstrated low sensitivity among KIT/PDGFRα wildtype GISTs. Comprehensive genomic profiling (CGP) is used to optimize the therapy selection due to its ability to detect undetected pathogenic biomarkers and allowing a more tailored approach to therapy in both primary and metastatic settings. Several treatable drivers including neurotrophic tyrosine kinase (NTRK) fusions have been identified by using CGP and could benefit patients with FDA approved therapies. Despite the advances of therapies and the known importance of CGP, the role of CGP is relatively low in patients with GIST. The present study reports results from Phase I of our multi-phase study, which will demonstrate the various genomic drivers that exist in this population and the potential impact of treatment trajectory for patients.

METHODS

Next generation sequencing (NGS)-based biomarker analysis was performed on tumor DNA and RNA focusing on wildtype GIST subgroups and included NTRK gene fusion. Patient recruitment involved The Life Raft Group (LRG) GIST Patient Registry members, direct patient outreach via phone and email, social media, and physician referral. Outcomes of Phase I study reports results from Phase I of our multi-phase study, which will demonstrate the various genomic drivers that exist in this population and the potential impact of treatment trajectory for patients.

RESULTS

- 104 patients expressed interest in the study. 55 (53%) patients were qualified for testing while 49 (47%) patients were not qualified.
- Out of the 49 unqualified, 18 (37%) did not meet residency requirements, 19 (39%) did not have any tissue available for testing and 12 (24%) patients already had CGP performed but were unaware or had not reported results to the patient registry. Tumor tissue from 55 eligible patients was processed through NGS.
- Out of the samples tested, 32 (58%) patients had a previous mutation test reporting KIT/PDGFRα wildtype, and 23 (42%) patients never had received CGP.
- 29 (53%) patients received a Test Not Performed (TNP), Quantity Not Sufficient (QNS) or showed results with Variants of Unknown Significance (VUS).
- Biomarkers were identified in 26 (47%) patients. Remarkably, NTRK ETV6-fusion positive was present in 2 (2/26; 8%). Half of the mutations detected were KIT mutations (13/26; 50%). PDGFRα mutation was present in 2 (2/26; 8%) patients, VUS in EGFRα mutation was detected in one patient. 3 (11%) patients showed an NFI mutation, with a dual mutation of SDHβ and NFI detected in one patient. SDHα mutation was present in 6 (23%) patients.
- With these results, 11 (42%) patients had to change or adjust their medication to ensure the most effective treatment plan.

CONCLUSIONS

- The vast majority of wildtype KIT and PDGFRα detected by basic mutational testing can and should be further classified.
- CGP found KIT (2) and PDGFRα (2) mutations in patients previously identified as KIT/PDGFRα Wildtype.
- CGP provides relevant data for a more accurate, individualized treatment plan for patients, and prevents patients from undergoing unnecessary therapies that will not work for their respective mutation.
- Phase II study is underway to explore additional genomic drivers and how targeted therapies can change the treatment trajectory and outcome for patients.
- Phase II will expand CGP to feature a 648 gene DNA panel sequence, Microsatellite Instability (MSI) status, Tumor Mutational Burden (TMB), and full transcriptome analysis by RNA sequencing. Patient-matched germline DNA will also be explored to further understand the genomic landscape in GIST.

OBJECTIVE

To present study reports results from Phase I of our multi-phase study, which will demonstrate the various genomic drivers that exist in this population and the potential impact of treatment trajectory for patients.

METHODS

CGP was performed on tumor DNA and RNA focusing on wildtype GIST subgroups and included NTRK gene fusion. The test featured a 20 gene panel including sequencing DNA of all the exons within the genes plus an additional 50 nucleotides at the 5’ and 3’ ends of each coding exon to detect splicing abnormalities.

RESULTS

Table 1. Summary of patient cohort from Phase I

<table>
<thead>
<tr>
<th>Gender</th>
<th>Ethnicity</th>
<th>%</th>
<th>Stage</th>
<th>%</th>
<th>Year of Specimen Collection</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>White, not hispanic origin</td>
<td>32 (60%)</td>
<td>100%</td>
<td>100%</td>
<td>&lt;2005</td>
<td>100%</td>
</tr>
<tr>
<td>Male</td>
<td>Hispanic</td>
<td>10 (19%)</td>
<td>100%</td>
<td>100%</td>
<td>2005–2009</td>
<td>100%</td>
</tr>
<tr>
<td>% Non-USA resident</td>
<td>26 (48%)</td>
<td>100%</td>
<td>100%</td>
<td>2005–2009</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

This table provides a summary of the patient cohort from Phase I, including gender, ethnicity, stage, year of specimen collection, and non-USA resident status.

REFERENCES


