Longitudinal mutational analysis of TP53 in plasma circulating tumor DNA in patients with solid tumors in a Phase I study of BI 907828, an MDM2–p53 antagonist

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Introduction

• Inactivation of p53 can occur due to TP53 mutations or downregulation of wild-type p53 by its primary negative regulator, MDM2.
• BI 907828, an MDM2–p53 antagonist, inhibits the interaction between the tumor suppressor p53 and MDM2. This restores p53 function, leading to p53 target gene induction that may result in cell cycle arrest or apoptosis in tumors with TP53-wt status.
• BI 907828 is currently being evaluated in a Phase Ia/b study in patients with advanced solid tumors (NCT03449381). During dose escalation (Phase Ia), BI 907828 demonstrated a manageable safety profile and early signs of efficacy.
• Here we present data from a longitudinal mutational analysis of TP53 using ctDNA; the objective was to identify if mutations in TP53 can be associated with possible acquired resistance to BI 907828.

Methods

• Blood sample collection for ctDNA analysis was optional, and sampled longitudinally from patients at baseline and every cycle until LAS.
• ctDNA was purified from plasma and analyzed using tumor-specific NGS (custom-made 8-gene panel using KAPA HypraCap technology, including TP53) to identify tumor-derived somatic mutations.
• The limit of detection was determined to be 0.5% mutant allele frequency; common polymorphisms were filtered out.
• Key inclusion and exclusion criteria have been presented previously.

Patients

Key baseline disease and patient characteristics for all pts enrolled to Phase Ia

| Arm A | Arm B
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<tr>
<td>Mean age, years (range)</td>
<td>53 (22–72)</td>
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<tr>
<td>Male, n (%)</td>
<td>15 (55.2)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>10 (50.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>15 (55.2)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>19 (65.5)</td>
</tr>
<tr>
<td>African American</td>
<td>1 (3.4)</td>
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<tr>
<td>ECOG PS 0/1/1 (n, %)</td>
<td>11 (37.1)/16 (52.9)/1 (3.4)</td>
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<td>Prior therapies, median (range)</td>
<td>2 (0–11)</td>
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Plasma samples for ctDNA analysis were collected from 46 (81%) patients:
• Baseline plasma samples from 26/54 (48%) patients and LAS samples from 36/54 (70%) patients were analyzed.

Results

• Baseline samples were available from 26/54 patients, whereas LAS were available from 36/54 patients.
• At baseline, most patients (75%) had no mutations in TP53; mutations were found in 4/26 (23%) samples.
• In two patient samples, mutations were found in both tumor and ctDNA, but concurrent results were limited to one patient.
• At LAS:
  - No mutations were found in 10/38 (26%) samples.
  - 1 mutation was found in 12/38 (31%) samples.
  - 2 mutations in 4/38 (10%) samples.
  - 3 mutations in 1/38 (3%) samples.
  - 4 mutations in 3/38 (8%) samples.

Lollipop plot showing ctDNA TP53 mutations at LAS

Key findings and conclusions

- This mutational analysis represents one of the first broad-based assessments of longitudinal ctDNA by NGS for TP53 from a clinical trial of an MDM2–p53 antagonist.
- Preliminary data suggest that BI 907828 does not systematically lead to broad acquisition of resistance by inducing alterations in TP53; however, this needs to be validated in larger data sets.

References


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