Adagrasib has previously demonstrated a manageable safety profile and clinical activity in patients with KRASG12C-mutated NSCLC. In the KRYSTAL-1 study, adagrasib capsules 600 mg orally BID (fasted state) were allowed – minus at least 1 hour before a meal and ≥1 hour before next meal; – with or without food; – with adagrasib swallowed whole, in a single intact胶囊, or as a split capsule, without crushing or chewing; – with ≥8 oz of water; – with or without antacids, H2 blockers, or proton pump inhibitors; – with or without other investigational agents; – with concomitant medications that do not interfere with CYP3A4 or P-glycoprotein; – with or without concomitant medications that are not strong CYP3A4 inhibitors or strong P-glycoprotein inhibitors; ▪ taken weekly on a fixed schedule; ▪ without skips; ▪ with a minimum interval of 24 hours between adagrasib capsules; ▪ complete the current cycle of adagrasib before starting any new cycle.

Key Eligibility Criteria

- Histologically or cytologically confirmed adenocarcinoma or non-small-cell lung cancer (NSCLC) with KRASG12C mutation
- Age ≥18 years
- ECOG PS 0–1
- Adequate organ function
- Baseline serum creatinine ≤1.5 × ULN or ≤1.8 × ULN in patients with baseline GFR ≤60 mL/min/1.73 m²
- Baseline AST ≤1.5 × ULN or ≤2.5 × ULN in patients with baseline GFR ≤60 mL/min/1.73 m²
- Adequate pregnancy and lactation status

Additional Safety Analyses

- Time to onset of treatment-related adverse events (TRAEs)
- Time to resolution of TRAEs
- Management of TRAEs

Results

Table 1. Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Trait</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race/ethnicity</td>
<td>47 (41%): African American, 18 (15%): Asian, 35 (30%): Caucasian, 4 (3%): other</td>
</tr>
<tr>
<td>Gender</td>
<td>61 (53%): female, 49 (43%): male</td>
</tr>
<tr>
<td>ECOG PS</td>
<td>0 (8%): 1 (4%): 2 (13%): 3 (1%): 4 (1%): missing</td>
</tr>
<tr>
<td>Baseline AST</td>
<td>38 (33%): ≤1.5 × ULN, 54 (47%): 1.5–2.5 × ULN, 14 (12%): ≥2.5 × ULN</td>
</tr>
<tr>
<td>Baseline ALT</td>
<td>3 (3%): &lt;1.5 × ULN, 43 (37%): 1.5–2.5 × ULN, 54 (47%): ≥2.5 × ULN</td>
</tr>
<tr>
<td>Previous systemic therapy</td>
<td>47 (41%): none, 49 (43%): 1 prior line, 2 (2%): 2 prior lines</td>
</tr>
<tr>
<td>Smoking history</td>
<td>47 (41%): never smoker, 32 (28%): past smoker, 3 (3%): current smoker, 3 (3%): former smoker</td>
</tr>
</tbody>
</table>

Time to Onset and Resolution of TRAEs

The median time to onset of TRAEs was 3 days (range, 1–213) for GI TRAEs and 22 days (range, 8–40) for non-GI TRAEs (Figsures 2a and 2b). Time to resolution after initial occurrence of GI TRAEs was 14 days (range, 1–106) for nausea, 10 days (range, 1–50) for vomiting, and 12 days (range, 1–106) for diarrhea. GI TRAEs that led to discontinuation in 8% patients. All other TRAEs that led to discontinuation in 3% patients.

Table 2. Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Trait</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRAEs leading to dose reduction, n (%)</td>
<td>38 (33%): nausea, 11 (10%): vomiting</td>
</tr>
<tr>
<td>TRAEs leading to dose interruption, n (%)</td>
<td>13 (11%): nausea, 11 (10%): vomiting</td>
</tr>
</tbody>
</table>

Table 3. TRAEs Leading to Dose Reduction or Interruption

<table>
<thead>
<tr>
<th>Trait</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP</td>
<td>1.00 (0.1</td>
</tr>
<tr>
<td>ALT increase</td>
<td>2.57 (0.7</td>
</tr>
<tr>
<td>AST increase</td>
<td>2.86 (1.0</td>
</tr>
</tbody>
</table>

Additional Practice-Informing Adverse Event Patterns and Management in the KRYSTAL-1 Phase 2 Study of Adagrasib (MRTX849) in Patients With KRASG12C-Mutated NSCLC


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Clinical trial registry number: NCT03785249

Summary

- Adagrasib, administered as capsules in a fasted state, demonstrated a manageable AE profile in patients with pretreated, advanced, KRASG12C-mutated NSCLC.
- Most TRAEs were grade 1–2, occurred as expected, and resolved, resulting in a low (7%) discontinuation rate.
- The most common TRAEs (GI-related, hematologic) were manageable with dose reductions/ interruptions and supportive medications.
- Adagrasib is currently being evaluated in a tablet formulation, administered both fasted and fed, which is hypothesized to improve tolerability, particularly for GI-related TRAEs.

References