Tipifarnib is a potent and highly selective farnesyl transferase (FT) inhibitor. All RAS isoforms (KRAS/NRAS/HRAS) are FT substrates. Oncogenic RAS pathway mutations (NRAS, KRAS, CBL, and PTPN11) are seen in approximately 30% of patients with chronic myelomonocytic leukemia (CMML) and are associated with a proliferative phenotype. Initial findings suggested tipifarnib may have greater activity in patients with Ras wild-type (wt) RAS, especially those with high CXCR4/CXCR2 levels. CXCR4/CXCR2 are involved in bone marrow homing of myeloid cells, and CXCL12/CXCR4 pathway is a potential target of FT inhibitors based upon work in T Cell activation.

**METHODS**

A phase 2 study (NCT02807272) evaluating the efficacy and safety of tipifarnib in patients with CMML and other MDS/MPN was performed. Eligibility criteria included:

- CMML: KRAS/NRAS wt
- MDS/MPN: high and low CXCR4/CXCR2

**Enrollment based on Key Eligibility Criteria**

Tipifarnib Treatment (N=44) 400 mg orally, BID on days 1-21 of 28-day treatment cycles

**Primary Objective:** Objective response rate (ORR) per MDS/MPN IWG criteria

- CMML: KRAS/NRAS wt
- MDS/MPN: high and low CXCR4/CXCR2

**Key Secondary Objectives:**

- Adverse event (AE) profile according to NCI CTCAE v 4.03
- PFS and OS at 1 year

**Fifteen (34%) patients had at least one serious treatment related AE**

- The most common prior anti-cancer therapies for patients with CMML were decitabine (29%) and hydroxyurea (29%). The most common prior anti-cancer therapies for patients with MDS/MPN were azacytidine (22%), hydrea (11%), and hydroxyurea (11%).

**Overall, data from this phase 2 study showed tipifarnib was reasonably well-tolerated.**

**RESULTS**

**Demographics**

- For CMML patients, 26 (70.3%) were CMML-1 and 11 (29.7%) were CMML-2
- The most common prior anti-cancer therapies for patients with CMML were azacytidine (22%), hydrea (11%), and hydroxyurea (11%).
- For patients with MDS/MPN, ORR was 25.0% including both high and low CXCR4/CXCR2 levels.

**Efficacy**

- For patients with CMML, ORR regardless of KRAS/NRAS mutational status was 21.9% (7/32); 14.3% (3/21) in KRAS/NRAS wt and 33.3% (3/9) in KRAS/NRAS mutant (mut). Duration of response was 14.6 months for KRAS/NRAS wt and not reached for KRAS/NRAS mut.
- For patients with MDS/MPN, ORR was 25.0% including both high and low CXCR4/CXCR2 levels.

**OS and PFS at 1 year**

<table>
<thead>
<tr>
<th>KRAS/NRAS</th>
<th>OS (N=21)</th>
<th>PFS (N=21)</th>
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<tbody>
<tr>
<td>KRAS/NRAS wt</td>
<td>14.4 months</td>
<td>Not reached</td>
</tr>
<tr>
<td>KRAS/NRAS mut</td>
<td>9.2 months</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

**Complete cytogenetic remission**

<table>
<thead>
<tr>
<th>KRAS/NRAS</th>
<th>No (N=1)</th>
<th>Yes (N=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS/NRAS wt</td>
<td>4.1 months</td>
<td>9.4 months</td>
</tr>
<tr>
<td>KRAS/NRAS mut</td>
<td>4.1 months</td>
<td>4.1 months</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

- Overall, data from this phase 2 study showed tipifarnib was reasonably well-tolerated.
- Modest efficacy was demonstrated in a difficult-to-treat population with limited therapeutic options.
- Although small numbers, the initial hypotheses surrounding KRAS/NRAS mutational status and CXCR4/CXCR2 levels were not supported.

**REFERENCES**