Preliminary results from an open-label, phase 2 study of tipifarnib in chronic myelomonocytic leukemia (CMML)

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BACKGROUND

Tipifarnib:
- Potent and highly selective inhibitor of farnesyl transferase (FT)
- All RAS isoforms (KRAS/NRAS/HRAS) are FT substrates, HRAS is uniquely dependent upon farnesylation alone. NRAS and KRAS are susceptible to redundant forms of prenylation and may lead to resistance to FT inhibition.
- Oncogenic RAS pathway mutations (NRAS, KRAS, CBL and PTEN) are seen in approximately 30% of CMML patients and are associated with proliferation phenotype.
- Previous trials without genetic selection yielded insufficient clinical activity to support registration, though evidence of single agent activity had been reported.
- In a prior study, 26/82 intermediate-risk pts (32%) responded to tipifarnib, including 21 pts with CMML-1 and 9 with CMML-2 (WHO Classification): 12 (15%) complete responses (CRs) and 14 (17%) hematologic improvements: 37 (45%) had stable disease (modified International Working Group criteria, 2006). In poor-risk CMML-2 (n = 9), tipifarnib yielded a 22% CR rate, with an overall median survival of 11.9 months (95% CI, 7.1-17.1).
- Manageable safety profile as single agent therapy (<25% treatment discontinuation).

METHODS

Phase 2 study designed to investigate the antitumor activity of tipifarnib in 20 evaluable pts with CMML (aged ≥18 yrs and ECOG PS 0-1) and retrospectively stratified based on KRAS/NRAS mutational status.

Study Design
- Tipifarnib 900 mg orally twice daily on Days 1 and 7; 15 – 21 in 28-day cycles
- Primary endpoint: Overall response rate (ORR) per Myelodysplastic/Multiple Myeloproliferative International Working Group (MDS/MPN IWG) criteria; with the probability that the TRUE underlying ORR rate exceeds historical control rate 0.1 computed via Bayesian methodology.
- Secondary endpoints: safety and tolerability, duration of response (DOR) and progression free survival (PFS). Biologic markers: sequential gene expression profiling of pre- and on-treatment bone marrow samples by RNASeq and flow cytometry based monoclonal and immune cell subset analyses.

Clinical trial information: NCT02807272

RESULTS

Patient Disposition

<table>
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<tr>
<th>Total Treated</th>
<th>CMML-1</th>
<th>CMML-2</th>
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<tr>
<td>n (%)</td>
<td>24 (100)</td>
<td>17 (70.8)</td>
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<tr>
<td>n (%)</td>
<td>7 (29.2)</td>
<td>4 (15.4)</td>
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Prior Lines of Therapy: Median (Range) 1 - 0 – 3

Total Discontinuations: n (%) 13 (54.2)

Reasons for Discontinuation:
- Adverse Event n (%) 4 (17)
- PI Decision n (%) 2 (8.3)
- Progressive Disease n (%) 6 (25)
- Withdrawal of Consent n (%) 2 (8.3)

Total Efficacy Evaluables n (%) 16:
- RAS wildtype (wt) n (%) 9 (56)
- RAS mutant (mut) n (%) 7 (44)

T5 pts (3 RAS mut, 2 RAS wt) discontinued prior to first response assessment; 3 pts (2 RAS wt, 1 RAS unknown) have not reached first response assessment

SAFETY & TOLERABILITY

- Toxicities were consistent with the known safety profile of tipifarnib.
- Grade ≥ 3 drug-related TEAEs occurring in ≥ 10% of pts were hematologic related: thrombocytopenia (38%), anemia (24%), neutropenia (14%) and leukopenia (17%). Additionally, one Gr 4 tumor lysis syndrome and one unusable Gr 4 acute hepatitis were observed.
- Myelosuppression was manageable with treatment interruption, dose reductions and/or transfusion support.
- Starting dose was reduced from 1200 mg to 900 mg twice daily on days 1-7 and 15 -21 of 28-day treatment cycles due to frequent myelosuppression and azotemia.

CONCLUSIONS

The primary endpoint of the study was met with an ORR of 33% in CMML patients whose tumors are RAS wildtype. These preliminary data may support further study of tipifarnib for the treatment of CMML.

Tipifarnib was generally well-tolerated. Most common treatment-related AEs (grade ≥ 3) were myelosuppression, including thrombocytopenia, anemia, neutropenia and leukopenia.

REFERENCES


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