The CXCL12/CXCR4 Pathway as a Potential Target of Tipifarnib: Preliminary Results from an Open-Label, Phase II Study in Relapsed or Refractory Peripheral T-cell Lymphoma

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BACKGROUND

Tipifarnib:
- Potent and highly selective inhibitor of Farnesyl Transferase (FT)
- FT catalyzes post-translational attachment of farnesyl groups required for localization of signaling molecules to the inner cell membrane.

CXCL12
- Chemokine that is essential for T cell homing to lymphoid organs and the bone marrow, and for the maintenance of immune cell progenitors.
- CXCL12 has been postulated to signal in part through HRAS, a signaling protein that is uniquely dependent on farnesylation for activity.

RESULTS

CLINICAL BENEFIT FROM TIPIFARNIB IS ASSOCIATED WITH CXCL12 GENOTYPE

Percent Reduction in SPD Over Time by CXCL12 Genotype

<table>
<thead>
<tr>
<th>CXCL12 Reference 3UTR 1</th>
<th>CXCL12 Variant 3UTR 3</th>
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</thead>
<tbody>
<tr>
<td>Reference</td>
<td>Tipifarnib</td>
</tr>
<tr>
<td>95% 90% 85%</td>
<td>85% 90% 95%</td>
</tr>
<tr>
<td>Not available</td>
<td>FXR2</td>
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</tbody>
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Results based on preliminary data as of 22 Nov 2017.

CLINICAL BENEFIT FROM TIPIFARNIB IS ASSOCIATED WITH CXCL12 EXPRESSION

CXCL12 expression was a specific biomarker of clinical benefit in patients receiving tipifarnib

CONCLUSIONS

- Encouraging activity of tipifarnib was observed in PTCL pts, particularly in those with tumors of AITL histology and high CXCL12 expression.
- Study is being amended to continue enrollment of pts with CXCL12+ PTCL. Enrollment in the AITL cohort is ongoing.
- Tipifarnib was generally well-tolerated. Most common treatment-related AEs (grade ≥ 3) were hematological, related, including neutropenia, thrombocytopenia, leukopenia, anemia and febrile neutropenia.

PATIENT DISPOSITION

Total Treated: 28

- AITL: 19 (100%)
- ALCL, ALK negative: 3 (16)
- PTCL, NOS: 15 (79)

Prior Lines of Therapy: Median (Range)

- Median: 4 (1 – 7)

Total Discontinuations: 17 (89)

- Reasons for Discontinuation: Progressive Disease: 16 (94)
- Withdrawal of Consent: 1 (6)

SAFETY & TOLERABILITY

- Toxicities were consistent with the known safety profile of tipifarnib.
- Grade ≥ 3 drug-related TEAEs occurring in ≥ 10% of pts were hematological related: neutropenia (74%), thrombocytopenia (58%), leukopenia (47%), anemia and febrile neutropenia (32% each) and lymphopenia (16%).
- Myelosuppression was manageable with treatment interruption, dose reductions, growth factor or transfusion support.
- The dose regimen was amended to 300 mg bid on days 1-28 of 28 day treatment cycles due to the observed tolerability profile of the alternate week regimen tested in stages 1 and 2 of the study.

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