Vecabrutinib is efficacious in vivo in a preclinical CLL adoptive transfer model

Billy Michael Chelliah Jebaraj1*, Annika Scheffold1*, Eugen Tausch1, Judith A. Fox2, Pietro Taverna3, Stephan Stilgenbauer1

1Department of Internal Medicine III, Ulm University, Ulm, Germany, 2Sunesis Pharmaceuticals, Inc. South San Francisco, CA, USA

*equal contribution

Introduction

- Vecabrutinib is an oral Bruton’s tyrosine kinase (BTK) inhibitor, inhibiting BTK with nanomolar potency
- It has high selectivity with IC50 < 100 nM in only 4 of 234 non-Tec family kinases
- It is a 1000-fold less potent in inhibiting EGFR in comparison toibrutinib

Taverna CLL

ibrutinib

Therapeutics

CLL

TCR

Therapeutics

Lymphoma

Cellular Therapy

Clinical

Copyright

© 2023 Nature Publishing Group

Comparison of routes of drug administration

- Investigated whether vecabrutinib administration through drinking water formulation would improve the PK profile
- C57BL6J mice (N=18) treated with either 50mg/kg BID PO (N=9) or 100mg/kg drinking water (N=9)
- 3 mice from each cohort were sacrificed after 1, 3, and 5 days of treatment and plasma drug concentration analyzed.
- Drinking water formulation achieved 25-45 fold lower plasma drug concentration compared to PO (Fig. 4).

Vecabrutinib decreases disease burden in Eq-TCL1 adoptive transfer model

- N=18 C57Bl/6 mice transplanted with splenic tumor cells from Eq-TCL1 mice.
- 1 week post-transplantation, the mice were treated with 50mg/kg vecabrutinib, twice daily PO (N=6) or 30mg/kg ibrutinib (drinking water; N=6) or vehicle control (N=6).
- Vecabrutinib and ibrutinib treatments decreased tumor burden with significant decrease in spleen weight (P=0.005), liver weight (P=0.005, P=0.010) and WBC count (P=0.002) compared to vehicle (Fig. 5a, 5b).
- % of CD5+ CD19+ tumor cells significantly decreased in blood (P=0.002) and spleen (P=0.003) upon vecabrutinib treatment while with ibrutinib treatment, decrease in tumor was observed in spleen and bone marrow (P=0.002; Fig. 5c, 5d).
- Tumor proliferation measured by K67 decreased upon drug treatment (data not shown).

Vecabrutinib treatment decreases Tregs in recipient mice

- % of CD4+ CD25+ FoxP3+ regulatory T cells (Tregs) significantly decreased upon treatment with vecabrutinib or ibrutinib in peripheral blood (P=0.006, P=0.004) and spleen (P=0.009, Fig. 7a).
- Tregs expressing maturation and activation markers CD103 and GITR significantly decreased in blood and spleen (Fig. 7b).

Vecabrutinib treatment prolongs survival

- To assess impact on survival a cohort of 18 C57Bl/6 mice were transplanted with 5 million tumor cells from Eq-TCL1 mice.
- Mice were treated with 50mg/kg vecabrutinib BID PO (N=6) or 30mg/kg ibrutinib (drinking water; N=6) or the vehicle (N=6).
- Mice treated with vecabrutinib and ibrutinib showed a significant increase in survival compared to vehicle (P<0.001, Fig. 8).

Efficacy of vecabrutinib in vitro on murine CLL tumors

- Sensitivity of murine CLL tumors to vecabrutinib in vitro was analyzed on 5 primary splenic tumors derived from Eq-TCL1 mice.
- Dose dependent increases in viability were observed in the presence or absence of 100ng/ml anti-IgM after 96 hours (Fig. 2).

Simulation of vecabrutinib PK profile in mice

- Pharmaco kinetic properties of vecabrutinib in mouse are inferior to those in human (half-life 1.24 hr in mouse vs. 2.17 hour in human).
- Simulations of concentration-time profiles of 50 mg/kg vecabrutinib in BID mice performed to identify the optimal dosing interval.
- Based on findings (Fig. 3), time interval of at least 8 hours between twice daily dosings was selected for further experiments

Comparison of TEC family and other kinases

<table>
<thead>
<tr>
<th>TEC Family Kinases</th>
<th>Other Kinases</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTK</td>
<td>IGFR1</td>
</tr>
<tr>
<td>TEC</td>
<td>ErbB2</td>
</tr>
<tr>
<td>HMRY</td>
<td>EGFR</td>
</tr>
<tr>
<td>CMEK</td>
<td>JAK3</td>
</tr>
<tr>
<td>CRK</td>
<td>JAK2</td>
</tr>
</tbody>
</table>

Vecabrutinib alters CD8 T cell architecture in recipients

- BTK inhibitors reshape tumor microenvironment, hence vecabrutinib impact on T-cell subsets studied.
- Fig. 6a: representative FACS plot showing gating strategy for CD4 and CD8 T-cells.
- Increase in %CD8+ T-cells was observed that was significant with ibrutinib (P=0.009) but not vecabrutinib (Fig. 6b).
- Among CD8 T-cells (Fig. 6c, 6d), vecabrutinib and ibrutinib resulted in expansion of the CD127+ CD44+ naïve CD8 T-cells in blood, bone marrow and spleen (P values 0.002).
- CD127+ CD44+ memory CD8 T-cells decreased but was significant only with vecabrutinib treatment (P=0.009).
- CD127+ CD44+foxp3+ effector CD8 T-cells decreased in blood (P=0.004), bone marrow (P=0.004) and spleen (P=0.002) upon vecabrutinib and ibrutinib treatments.

Conflicts of interest disclosures

Tausch, Roche AG; Other: Advisory board, lectures; Gilead: Consultancy, Other: Travel grants; Celgene: Consultancy, Other: Travel grants; AbbVie: Consultancy, Other: Travel support, expert testimony; Seqens Pharmaceuticals: Employment; Amgen: Other: Employment; Sunesis Pharmaceuticals: Employment; Stilgenbauer; Gilead; Celgene; Ageron; Genentech; Boehringer-Ingelheim; Sanofi; Hoffman La Roche; Mundipharma; Pharmaciegen: Genzyme; Janssen; Novartis; AbbVie; GSK; Consultancy, Honorary membership on an entity’s Board of Directors or advisory committee, Research Funding.