LOXO-292, a Potent, Highly Selective RET Inhibitor, in Multi-Kinase Inhibitor-Resistant RET Fusion-Positive Lung Cancer Patients with and without Brain Metastases

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Repurposed “RET Inhibitors”: poor RET coverage in humans

<table>
<thead>
<tr>
<th>MKI</th>
<th>Approved Dose</th>
<th>Toxicities</th>
<th>RET Inhibition (Human C\text{max})*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cabozantinib</td>
<td>140 mg QD</td>
<td>Diarrhea, PPE, ↓weight/appetite, fatigue, hypertension</td>
<td>51%</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>300 mg QD</td>
<td>Diarrhea, hypertension, QT prolonged, fatigue, rash</td>
<td>24%</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>24 mg QD</td>
<td>Diarrhea, hypertension, ↓weight/appetite, fatigue, proteinuria</td>
<td>47%</td>
</tr>
<tr>
<td>Alectinib</td>
<td>600 mg BID</td>
<td>↑ALT/AST/GGT/Bilirubin, anemia, nausea/vomiting, diarrhea</td>
<td>32%</td>
</tr>
</tbody>
</table>

*cellular (phospho-RET) inhibitory concentration corrected for human plasma protein binding and published human PK
LOXO-292: potent and selective RET inhibition

- Rationally designed, informed by proprietary crystallography insights
- Highly selective
- Fusion- and mutation-independent RET inhibition
  - e.g. KIF5B-RET, CCDC6-RET
  - C634W, M918T, V804L/M
    (gatekeeper—acquired resistance)
- Favorable drug-like properties
LOXO-292’s potential in lung cancer

(1) Naïve RET Fusion

(2) Potential acquired resistance

(3) Brain metastases

KIF5B-RET (3T3)

CCDC6-RET V804M (PDX)

CCDC6-RET orthotopic brain (PDX)
LOXO-292 Phase 1 study in progress

- 28 patients enrolled to 4 dose levels (first patient dosed May 2017)
- No DLTs
- PK dose proportional and consistent with significant RET target engagement

September 27, 2017 data cut-off date, cellular (phospho-RET) IC$_{50}$/IC$_{90}$ corrected for human plasma protein binding
Patient 1: CCDC6-RET fusion

- 63-year old woman with advanced NSCLC: prior surgery, radiation, and chemotherapy

- After identification of CCDC6-RET fusion, received RXDX-105 for 7 months and then progressed

- First LOXO-292 patient treated with RET fusion lung cancer, on Phase 1 trial (20 mg QD)

- Confirmed PR by RECIST 1.1 (-44%) on 20 mg QD, dose escalated to 20 BID and currently 40 mg BID, remains on therapy in month 5
Patient 2: KIF5B-RET fusion

- 40-year old woman never-smoker with advanced NSCLC: 3 lines of chemotherapy, whole brain radiation, anti-PD1 antibody
- After identification of KIF5B-RET fusion, received 600 mg BID alectinib (PR, 7 months), increased to 900 mg BID for progressive brain metastases
- Treated with LOXO-292 under Single Patient Protocol due to symptomatic brain metastases (first LOXO-292 patient treated with RET fusion lung cancer with brain metastases)
- LOXO-292 administered by PK-guided intra-patient dose escalation, 20 mg/60 mg/100 mg BID
Patient 2 pharmacokinetics at current dose

- Patient experienced dramatic clinical improvement
- Neurologic symptoms (memory loss, gait unsteadiness) improved within 7 days
- Confirmed systemic PR (-64%, RECIST 1.1) and CNS response (-89%, RANO-BM)
- Patient remains on therapy in month 4

**cellular (phospho-RET) IC$_{50}$/IC$_{90}$** corrected for plasma/brain protein binding and estimated CNS penetration
Systemic tumor response

Pre-treatment

LOXO-292 at 2 mo.
Intracranial tumor response

Pre-treatment

LOXO-292 at 3 mo.
Intracranial tumor response

Pre-treatment

LOXO-292 at 2 mo.
Conclusions

• LOXO-292: RET inhibition in ongoing Phase 1 trial already greater than multikinase (MKI) inhibitors
  • Well-tolerated with no DLTs
  • Biologically relevant doses

• Proof concept anti-tumor efficacy in patients with RET-fusion NSCLC
  • Heavily pre-treated and MKI-experienced patients
  • With/without brain metastases

• Phase 1 study currently enrolling patients
  • 855-RET-4-292 (855-738-4292)
  • clinicaltrials@loxooncology.com
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